	Date of ɔue	Date of Return

NUTRITION

and

HORMONES

2515 ① nutrition
② endocrine glands
③ pancreas
④ thyroid gland
⑤ adrenal cortex
⑥ gonadal hormones
⑦ anterior hypophysis

Publication Number 11

AMERICAN LECTURE SERIES

A Monograph In

AMERICAN LECTURES IN ENDOCRINOLOGY

Edited by

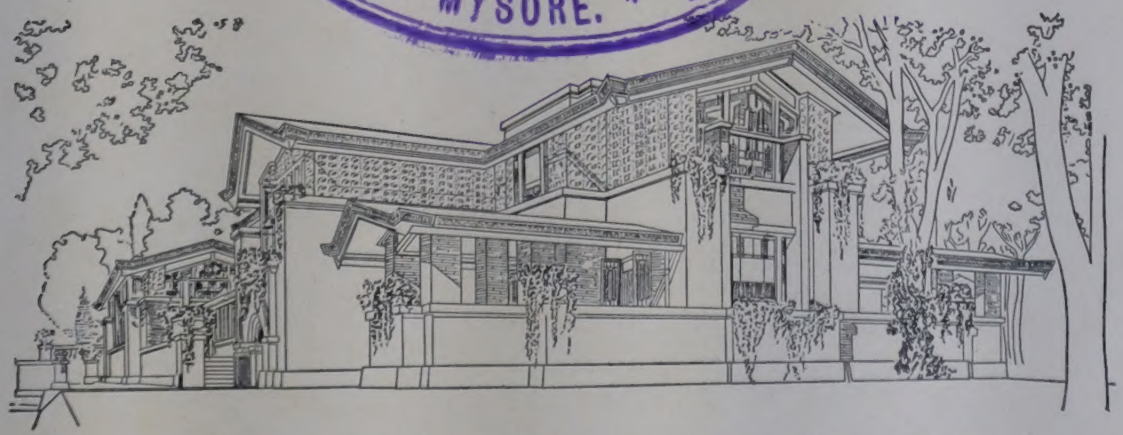
WILLARD O. THOMPSON, M.D.
Clinical Professor of Medicine
University of Illinois College of Medicine
Managing Editor, Journal of Clinical Endocrinology
Chicago, Illinois

NUTRITION
and
HORMONES

By

LEO T. SAMUELS, PH.D.

Professor of Biochemistry
University of Utah School of Medicine
Salt Lake City, Utah



CHARLES C THOMAS · PUBLISHER

Springfield · Illinois · U.S.A.

CHARLES C THOMAS · PUBLISHER
BANNERSTONE HOUSE
301-327 EAST LAWRENCE AVENUE, SPRINGFIELD, ILLINOIS

Published simultaneously in The British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS, LTD., OXFORD, ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS, TORONTO

FIRST PRINTING

Printed in the United States of America

CONTENTS

NUTRITION
and
HORMONES

Introduction

The endocrine glands are specific chemical factories upon which the whole organism depends. But, like all factories, their ability to produce useful products depends on the raw materials they receive. In discussing the relations between nutrition and the endocrine system, therefore, we are dealing with the relationship between raw materials and manufactured products.

Not only does the subject cover this problem, but both the products of the endocrine system and the foods themselves are used as essential materials in certain cells. Thus nutritive effects on the endocrine system may indirectly affect the function of other tissues. A properly controlled experiment in nutrition must distinguish between the direct results of the nutritive change and those mediated through the endocrine system. Conversely, a study of the metabolic effects of the hormones must take into consideration any change in food intake which itself would influence metabolism in the body. In medicine this interplay should be kept constantly in mind both in diagnosis and therapy.

Problems in nutrition cannot be approached without at the same time considering the rôle of hunger. How is it controlled? The regulation of hunger by the hypothalamus was first clearly demonstrated by Smith (1) in rats. He found that obese rats were not obtained if the hypophysis alone was removed; but if the hypothalamus was also damaged, obesity resulted. He then proceeded to damage the hypothalamus, leaving the hypophysis intact, and found that obesity still occurred. The same result has been observed in dogs, monkeys, and cats. Brobeck, Tepperman and Long (2) showed that the obesity was primarily due to increased food intake. If the food given the animals was limited to that of normal rats, there was no obesity. However, the animals with hypothalamic damage would eat the normal amount of food in a very short time. *The hypothalamus, therefore, appears to contain a center which depresses hunger.*

Another important observation which Long and his co-workers (3) made is that the rate at which food is eaten affects its utilization. Normal animals eat small amounts of food throughout the day. Rats were trained by Long to eat their entire daily ration in a two-hour

period. These animals gained more weight on the same amount of food than did those rats which ate throughout the day. This illustrates *the importance of eating habits* in influencing the interpretation of nutritional problems.

The tone of the gastric musculature is also an important regulator of hunger. The decreased food intake in thiamine-deficient rats appears to be due to the decreased tone of the gastro-intestinal musculature (4). If an animal is fed a thiamine-deficient diet by stomach-tube in quantities adequate to maintain normal growth when thiamine is added, there is a gradual swelling of the abdomen until the animal dies because the greatly distended stomach interferes with the circulation and the respiration. Very little of the food passes from the stomach into the intestine. In thiamine-deficiency, therefore, the loss of hunger is a compensatory phenomenon due to the decreased tone of the gastric muscle.

Increased energy expenditure also seems to stimulate hunger. This is seen, of course, in every growing animal. An example of loss of this stimulus is in the animal (including the human) with pituitary destruction but an intact hypothalamus (5). Such an individual has a decreased food intake but, if it is forced to consume normal amounts of food, the material is absorbed and the excess deposited as fat (Table 1). Stimulating growth in such an animal by injection of pituitary hormones will also stimulate the desire for food. In understanding the interplay between the hormones and nutrition, the effects on hunger and on eating habits must, therefore, be distinguished from those acting directly on the fundamental metabolism.

Pancreas

The relation between the endocrine system and nutrition was perhaps first clearly recognized with the demonstration of the internal secretion of the pancreas. In the total absence of insulin, carbohydrate is largely lost in the urine, protein is rapidly broken down, and the disturbances in the utilization of carbohydrate lead to utilization of fat by the most rapid means possible: its conversion into acetone bodies by the liver and their oxidation by the cells of the tissues in general. Some glucose is still used by the tissues of diabetic animals, but many workers do not agree with Soskin (6) that at ordinary diabetic blood

sugar levels the consumption of glucose represents as great a proportion of the metabolism as in normal animals. A large part of the energy is furnished by the circulating acetone bodies.

The administration of *insulin* definitely increases the utilization of glucose and its conversion to muscle glycogen, while it decreases

TABLE 1. CALORIC BALANCE ON YOUNG FORCE-FED RATS WITH AND WITHOUT THE HYPOPHYSIS

Rat Number	4	5	7	8	10	11
Type of preparation	Hypophysectomized	Control	Hypophysectomized	Control	Hypophysectomized	Control
Days on diet	22	22	32	32	54	54
Total intake, calories	725.4	745.1	1053.9	1053.9	1822.5	1822.5
Unabsorbed food, calories						
Carbohydrate	27.5	19.3	37.8	27.3	74.0	47.2
Protein	21.5	14.6	24.3	17.5	41.1	25.9
Fat	72.1	50.9	65.2	47.4	138.9	86.3
Total unabsorbed calories	121.1	84.8	127.3	92.2	254.0	159.4
Increase in N stored calories	6.9	34.2	16.2	33.4	17.9	61.4
Increase in fat stored calories	96.7	80.6	245.2	34.1	398.9	81.6
Total caloric increase	103.6	114.8	261.4	67.5	416.8	143.0
Calories used	500.7	545.5	665.2	802.0	1155.7	1520.1
Total metabolic rate Cal./day	22.8	24.8	20.8	25.1	21.4	38.2
Total metabolic rate* Cal./sq. m./day	10.3	10.7	10.0	11.6	9.3	12.1

* This is not basal metabolic rate, but the average total calories used in a day. (L.T. Samuels, R. M. Reinecke and K. L. Bauman, *Endocrinology* 33: 87, 1943.)

gluconeogenesis from protein. Price, Cori and Colowick (7) have been able to demonstrate in simple systems one means by which insulin brings about this effect. They have shown that a pituitary extract decreases the catalytic activity of hexokinase whereby circulating glucose is converted into phosphorylated glucose in the muscle and thence into glycogen. Insulin introduced into the simple system of hexokinase - glucose - adenosine triphosphate - pituitary extract inhibits the action of the pituitary hormone (Figure 1). Rice and Evans (8) also have published evidence that, in simple systems, insulin will increase the oxidation of pyruvic acid.

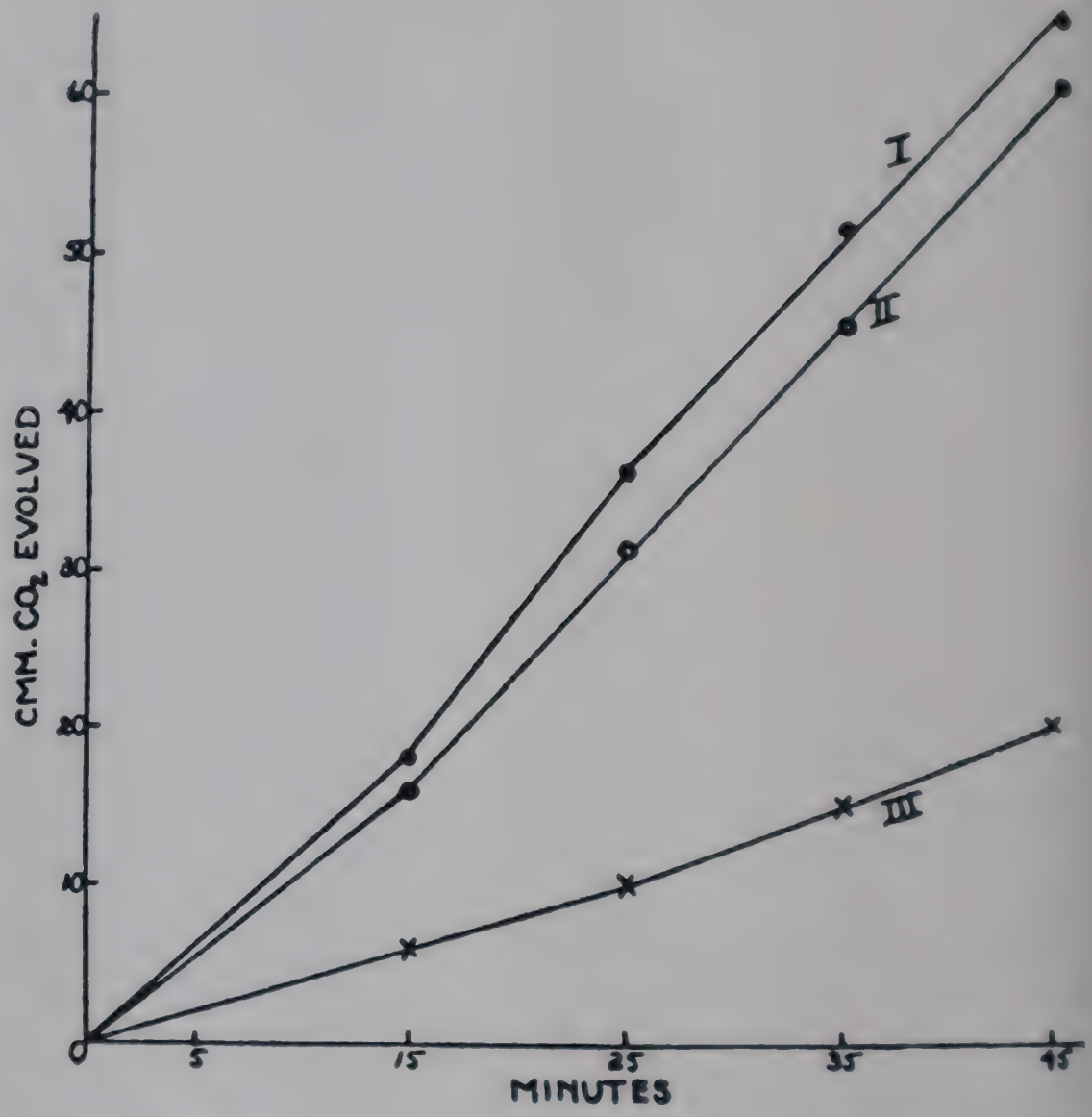


FIG. 1. The effect of anterior pituitary extract (K fraction) and insulin on purified muscle hexokinase.

The hexokinase activity is measured manometrically. The disappearance of adenosine triphosphate was determined chemically at the end of the experiment and was found to be in agreement with the results obtained by the manometric procedure. Curve I, hexokinase; Curve II, hexokinase 400 gamma APE 75 gamma insulin; Curve III, hexokinase 400 APE.

(W. H. Price, C. F. Cori and S. P. Colowick: *J. Biol. Chem.*, *160*:633, 1945.)

We have here then a substance which greatly influences the utilization of one of the major foodstuffs. This was recognized many years ago; and until the discovery of insulin, the only means by which diabetes could be even partially controlled was by a great reduction in the amount of carbohydrate in the diet. At the same time the

acidosis, due to increased utilization of fat by means of acetoacetic and beta-hydroxy butyric acid, required careful control. With insulin available, however, the ability to utilize carbohydrates can be restored.

The problem of maintaining nutrition in controlled diabetics remains, for there appears to be a quantitative relation between the amount of insulin and the carbohydrate which can be utilized. The most desirable level of carbohydrate in the diet and the level at which blood sugar should be maintained by insulin are still subjects of debate between specialists in this field, and most workers still control mild diabetes by reduction in carbohydrate intake.

Associated with the decreased utilization of carbohydrate in the insulin-deficient individual is a decreased need for the accessory factors associated with carbohydrate metabolism. Thiamine, niacin, and perhaps pantothenic acid act as coenzymes in carbohydrate oxidation systems. The need for these vitamins is reduced in the diabetic just as it is in the normal animal on a high fat, low carbohydrate diet. On administration of insulin the intake of the vitamin B complex should be high, since tissue concentrations must be restored as well as providing for the increased utilization as carbohydrate is metabolized.

Not only is the need for vitamins of the B complex dependent on the available insulin, but the effectiveness of insulin appears to be influenced by any deficiency of these factors. Martin (113) found that depancreatized dogs on a vitamin B-deficient diet became resistant to insulin. Elsom, Lukens, Montgomery and Jonas (114) found a progressive decrease in the response to insulin as deficiency of the B complex was produced experimentally in a woman (Table 2). On feeding riboflavin and thiamine, the subject became abnormally sensitive to insulin. Biskind (9) feels that vitamin therapy is effective in decreasing the hormone requirement of insulin-resistant diabetes.

There are certain dangers in the dietary control of diabetes. The pituitary gland is sensitive to both caloric and protein deficiencies. Limitation of food intake on a restricted diet, coupled with the increased protein breakdown associated with insulin deficiency, may lead to secondary disturbances in gonadal function and in growth because of pituitary insufficiency. This is particularly true during the

adolescent period. Two cases illustrating this condition are given in the section on the pituitary gland.

Excessive insulin production leads to the opposite effect on nutrition. There is a constant demand for carbohydrates to maintain the blood sugar level. The excess glucose not converted into glycogen and oxidized is converted into fat. All phases of carbohydrate metabolism are accelerated. As a consequence, along with the increased need

TABLE 2. BLOOD SUGAR, BEFORE AND FOLLOWING THE SUBCUTANEOUS ADMINISTRATION OF 2.5 UNITS OF INSULIN IN THE DIFFERENT EXPERIMENTAL PERIODS ON FEMALE SUBJECT, AGE SIXTY YEARS

Date 1938	Blood Sugar						
	Initial	½ hour	1 hour	2 hours	3 hours	Maximal decrease in blood sugar*	
	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	per cent	
March 11	71	66	56	59	61	21	Deficient diet
March 25	70	70	63	68	78	10	
April 29	66	76	66	70	76	0	
May 6	77	53	49	56	62	36	Deficient diet+thiamin
May 13	66	64	65	65	66	3	
May 17	68	61	59	58		15	
May 27	86	58	44	52	56	49	Deficient diet+thiamin+riboflavin
May 31	131	101	67	48	62	63	

* Maximal decrease in blood sugar is here represented as the per cent fall from the initial blood sugar to the lowest value obtained in the test.

(K. O. Elsom, F. D. W. Lukens, *J. Clin. Investigation* 19: 153, 1940.)

for carbohydrate there is an increased need of thiamine, niacin, and other accessory factors associated with carbohydrate metabolism. Thiamine deficiency can develop in such individuals when the intake would be ample for a normal person.

The work of Best, Haist, and Ridout (10) has established the importance of the diet in regulating the production of insulin by the pancreas. Apparently a high fat diet, fasting, or insulin administration lowers the insulin content of the pancreas below that on a high

carbohydrate diet alone. High protein diets give intermediate values. The conclusion seems justified that the carbohydrate available in the diet determines the production of insulin by the normal islet cells of the pancreas. Malignant cells of islet origin are apparently less susceptible to changes in carbohydrate level.

If insulin production is stimulated to too high a level, the islet cells may be exhausted. Lukens (11) has shown that this occurs when large doses of anterior pituitary diabetogenic extract are given to partially depancreatized rats. Houssay (12) has demonstrated the same effect in rats when total catabolism, and therefore conversion of protein to glucose, has been increased by administration of thyroid hormone. In neither of these cases, however, were the investigators able to obtain exhaustion diabetes in rats with completely normal pancreases.

The rôle of the vitamins in insulin production is still uncertain. The problem which arises in much of this type of work is to distinguish the effect of general inanition from that of the vitamin. In the case of thiamine, reduction in insulin production accompanies deficiency, but this was found to be due to the inanition rather than thiamine *per se* since animals limited to the same food intake but receiving ample thiamine showed a similar drop in insulin content (10). The insulin content of the pancreas of ascorbutic guinea pigs is reported to be reduced to one-eighth of the normal (13, 14), but no control of food intake by paired feeding is reported. An excellent review of the effect of diet on the insulin content of the pancreas has been published by Haist (15).

Thyroid Gland

The thyroid gland affects nutrition through its influence on absorption, on the basal metabolic rate, and on anabolic processes.

The rate of absorption of those substances which pass through the intestinal wall by other means than simple diffusion is dependent upon the presence of the thyroid hormone. Althausen (16) has shown that the absorption of sugars and fatty acids is delayed in myxedematous patients and in thyroidectomized rats. If thyroid hormone is administered in excess, the rate of absorption of these substances is increased above normal (Table 3). This increased rate of absorp-

tion of glucose in hyperthyroid subjects accounts for the high oral glucose tolerance curves which are often seen (17). Unless fasting blood sugars are above the normal level, such tolerances do not indicate diabetes but simply the increased rate of passage from the intestinal tract. The converse is true in myxedema. These patients often show a flat glucose tolerance curve when the carbohydrate is administered by mouth. Much more can be learned regarding glucose

TABLE 3. INTESTINAL ABSORPTION OF CARBOHYDRATES IN NORMAL, HYPERTHYROID AND THYROIDECTOMIZED RATS

Experimental condition	Substance administered	Amount absorbed in one hour per 100 gm. of weight, mg.
Normal	Dextrose	171±14*
Hyperthyroid	Dextrose	284±30
Thyroidectomized	Dextrose	91± 5
Normal	Galactose	187±27
Hyperthyroid	Galactose	273±18
Normal	Starch	126±24
Hyperthyroid	Starch	196±14

* Standard deviation.
(T. L. Althausen, *J.A.M.A.*, *115*: 101, 1940.)

utilization in patients with thyroid disturbance if intravenous tolerances are used.

The absorption of amino acids does not seem to be disturbed by changes in thyroid function (16). Disturbances of absorption cannot, therefore, account for failure of growth in hypothyroid individuals.

Aside from the effect on absorption, the thyroid gland does not seem specifically to affect carbohydrate metabolism as a whole. Russell (18) showed that in hypophysectomized animals the administration of thyroxin restored the reduced absorption in the gut, but did not change the distribution of absorbed carbohydrate from the pattern seen in untreated pituitary deficiency. In such animals any abnormalities in carbohydrate metabolism due to the treatment would be most easily noticed because the compensatory adjustments controlled by pituitary hormones are eliminated.

The most widely known effect of the thyroid hormone is its effect on the oxidative metabolism of the cells of the resting organism. Apparently the thyroid hormone increases the catabolic rate and the output of energy of practically every cell of the body. Its outward evidences are well known in the mental sluggishness and muscular slowness of the hypothyroid individual, together with the extreme nervousness and muscular over-activity of the hyperthyroid subject. Because of this effect less food is needed in hypothyroidism and more in hyperthyroidism. This is particularly true of the energy yielding foods, but it is also the case with proteins.

The interplay of appetite in the disturbances of the thyroid gland must be taken into consideration in the thyroid patient. It is rare to see a truly obese individual with hypothyroidism. The slower emptying of the intestinal tract, together with the decreased protein anabolism, leads to a reduction of hunger which in some cases may overcompensate for the reduced metabolism. On the other hand in severe hyperthyroidism the appetite, while voracious, is not stimulated to the point of energy balance so that ordinarily there is a tendency to catabolize body protein in addition to that in the food.

The thyroid hormone is of fundamental importance in protein synthesis. The thyroidectomized animal or the cretin child does not grow: it becomes pot bellied but it is rarely obese. Administration of pituitary growth hormone to thyroidectomized animals has less effect than in normal animals (19), (Figure 2). Evans and co-workers (20) have found that in hypophysectomized rats the administration of a combination of the growth hormone and thyrotrophic hormone is synergistic; the combined effect is greater than the sum of either alone. While the clear-cut evidence of the interrelationships of these two important factors in growth has only recently been worked out, clinical experience had long ago demonstrated the importance of thyroid function in growth even where the thyroid was not the primary deficiency involved.

While adequate thyroid hormone is necessary for growth in young animals, excess will cause *loss of weight* in adults. The failure to maintain weight often is due to a limitation in the intake of some essential factor. The increased catabolic processes involve increased wear and tear on the already existing structures and, therefore, the

amount of essential substances necessary for simple replacement in creases. This has been particularly well demonstrated by Drill an co-workers in the case of thiamine, pyridoxin and pantothenic aci (21). Weight restoration can often be achieved by addition of thes

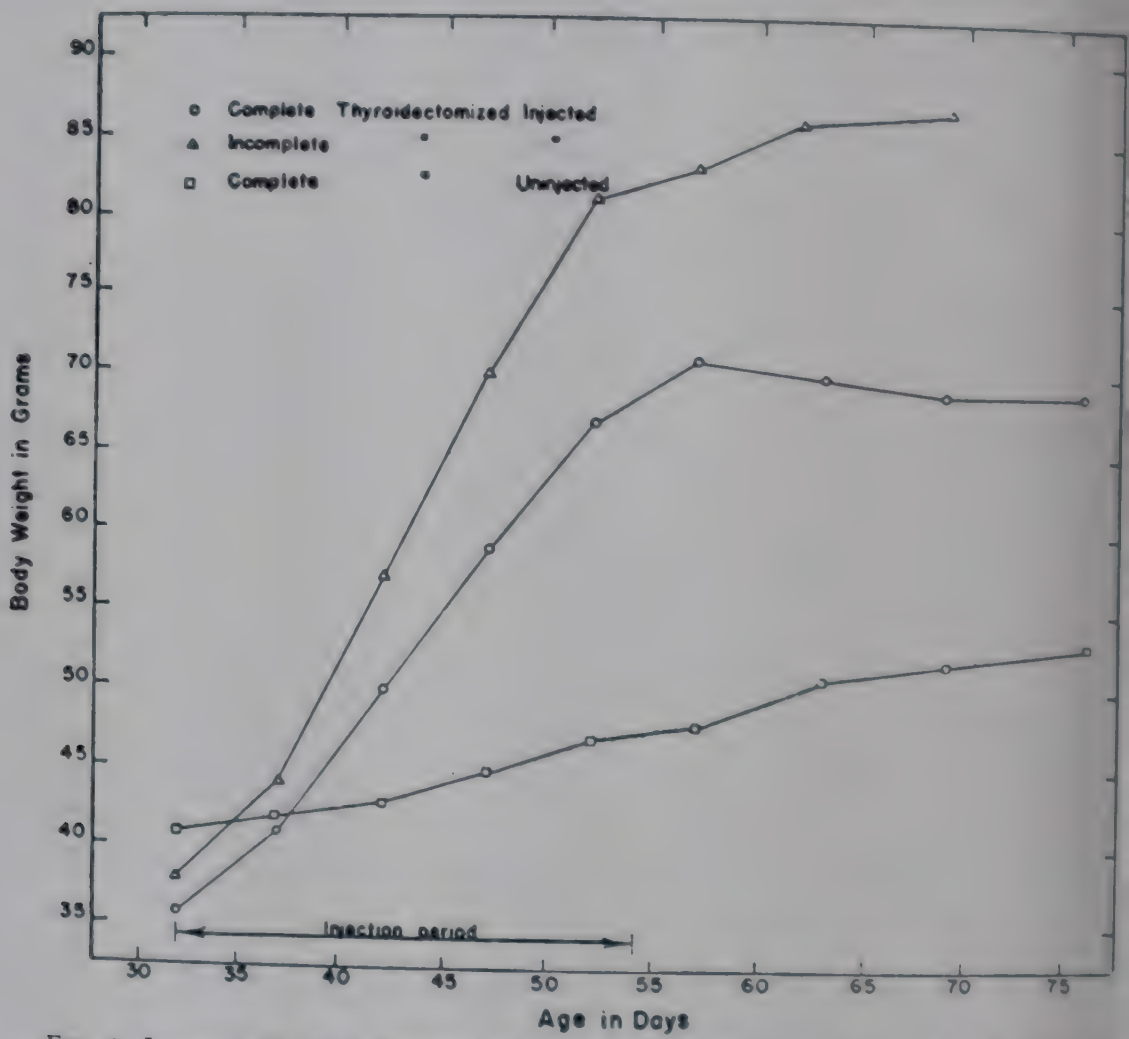


FIG. 2. Increase in body weight of eleven growth hormone injected and seven uninjected thyroidectomized rats during a 23-day experimental period beginning at 32 days of age. The body weight increase of three injected rats subsequently found to have been incompletely thyroidectomized is also shown.

(R. O. Scow and W. Marx: *Anat. Rec., 91*:227, 1945.)

factors (22). Eventually, however, with increasing hyperthyroidism the increased rate of catabolism exceeds the stimulus to hunger, and in spite of the high quality of the diet a positive nitrogen balance goes over into a negative one. A limit is thus put on the thyroid as an anabolic factor.

The influence of the thyroid gland on *the metabolism of the cells* in various organs has an effect on certain specific processes which

affect nutrition. In the thyroidectomized animal carotene is not converted to vitamin A at a normal rate (23, 24, 25). The liver seems to be unable to split the carotene chain. Vitamin A deficiency may, therefore, be a complication of hypothyroidism, on a diet which would normally supply a sufficient amount of its precursors. Carotenemia is also often present. Drill (26) has reviewed the literature on the relation of thyroid function to the vitamins.

Not only does the thyroid affect *nutrition,* but it, in turn, is affected by nutrition. Iodine deficiency was shown many years ago to be responsible for the development of simple goiter. This enlargement is apparently due to the increased size and number of cells associated with more efficient utilization of the iodine available. The importance of maintaining an adequate iodine supply is so well known today that it need not be discussed in detail.

Animals on a diet insufficient to maintain nitrogen and weight balance or during complete starvation have reduced basal metabolic rates. Hundhausen (27) claims that this is due specifically to vitamin B_1 deficiency, but the work of Drill would indicate that it is primarily due to caloric restriction. The effect is, apparently, directly on the hypophysis and only indirectly on the thyroid gland through reduced production of the thyrotrophic hormone.

Vitamin A seems to be antagonistic to the thyroid gland. As early as 1923 McCarrison (28) reported that administration of cod liver oil would delay metamorphosis of tadpoles receiving a high iodine intake. This has been shown to be due to the vitamin A content of the oil (29).

Specific diets affect thyroid function. This was first observed when a cabbage diet produced goiter (30) in rabbits. Rape seed and soy bean diets also had the same effect (31, 32). The active principles in these various diets appear to be nitriles. Methylcyanide (acetonitrile) was found by Marine (33) to be a definite goitrogenic agent. It indirectly stimulates greater production of thyrotrophic hormone by interfering with the up-take of iodine by the thyroid gland (51). Human diets are rarely, if ever, high enough in these substances to cause the development of obvious goiter, but a few cases have been reported when potassium thiocyanate has been used as a therapeutic agent.

TABLE 4. EFFECTS OF PARA AMINOBENZOIC ACID (PABA) AND THIOURACIL ON BODY GROWTH, THYROID WEIGHT, OXYGEN CONSUMPTION AND RESISTANCE TO REDUCED BAROMETRIC PRESSURES (190 MM. Hg) OF ADULT MALE RATS. MEAN FIGURES ARE GIVEN WITH THEIR STANDARD ERRORS

Days treat.	Paba					Thiouracil				
	No. anim.	Wt. gain (gm.)	Thyr. wt. (mg.)	O_2 Cons. (cc./cm.^{2}/hr.)	Survival time (mins.)	No. anim.	Wt. gain (gm.)	Thyr. wt. (mg.)	O_2 Cons. (cc./cm.^{2}/hr.)	Survival time (mins.)
19–22	12	34	26.2±1.2	0.75±0.03	61.2±8.3 5*	12	19	53.5±2.0	0.71±0.03	>120 11*
26–30	13	46	37.0±2.0	0.73±0.02	83.8±6.3 7*	12	26	67.8±3.2	0.65±0.015	>120 12*
40–45	12	52	41.2±3.8	0.69±0.02	78.3±6.1 6*	12	27	74.3±3.1	0.67±0.02	>120 12*
				Controls						
0	36	(28)† (40) (50)	17.2±0.32	0.97±0.01	35.1±3.2 4*					

* Number of animals surviving the two-hour exposure to 190 mm. Hg.

† Weight gains 20, 28, and 42 days after start of the experiment.

(A. S. Gordon, E. D. Goldsmith and H. A. Charipper, *Endocrinology*, 37: 223, 1945.)

Para aminobenzoic acid, a doubtful member of the vitamin B complex, when administered in large dosage, causes thyroid hyperplasia associated with a reduction in metabolic rate (34, 35). The data of Gordon *et al.* are given in Table 4. At the same time changes which are ordinarily associated with thyroidectomy occur in the anterior hypophysis. Apparently, para aminobenzoic acid interferes with the enzyme systems involved in the synthesis of thyroxin from iodine and tyrosine.

Thiouracil, the drug now being widely used in the treatment of hyperthyroidism, acts in a similar manner. Since iodine cannot be combined into hormonal form, the symptoms of iodine deficiency exist in the presence of ample iodine in the diet.

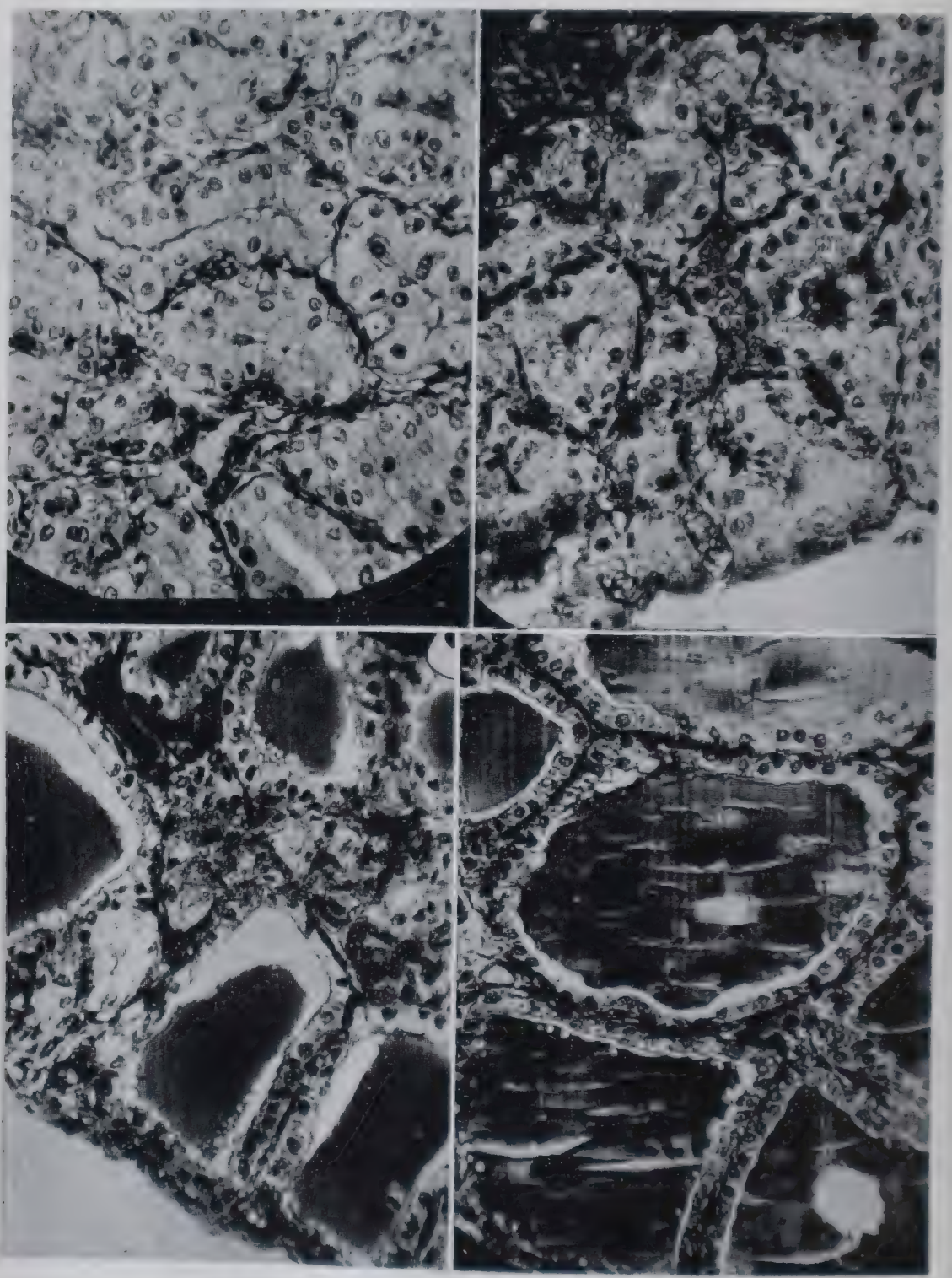
If estrogens are administered to rats on a diet low in iodine, Gassner *et al.* have shown that hyperplasia of the thyroid gland is largely prevented, and colloid is stored even though the iodine content is very low (36). Stilbestrol seems more effective than estrone (Figure 3). This may be a case of the estrogens depressing pituitary function in general more than iodine restriction stimulates thyrotrophic hormone formation.

It is obvious then that the function of the thyroid must be considered in evaluating the nutrition of an individual. *In hyperthyroidism* there should be diets high in calories, in the vitamin B complex, in methylating agents (choline, methionine) and in the essential amino acids. On the other hand, *in hypothyroidism* these substances are not needed to the same extent, but thought must be given to an adequate source of vitamin A as distinguished from vitamin precursors. The importance of the thyroid hormone in connection with protein anabolism must always be considered when disturbances in growth are present. Finally, the effect of diet on the gland itself must be kept in mind, particularly in those individuals with dietary aberrations.

Adrenal Cortex

The adrenal cortex affects nutrition through its influence on endogenous protein metabolism. The effect is not marked, however, except under stress or during fasting. An adrenalectomized rat can handle diets of widely different composition if salt or desoxycorticosterone is administered. Whether adrenalectomized animals on carbohydrate-

A B



C D

deficient, high protein diets can be successfully maintained is under some dispute. Eversole (37) was unsuccessful with desoxycorticosterone alone. On the other hand Segaloff (38) reports good growth and survival when desoxycorticosterone pellets were implanted and a diet free from carbohydrate and containing crude casein was fed. When a high fat diet very low in both protein and carbohydrate is fed by stomach tube, adrenalectomized rats will survive for several days but not so long as the normal animal (39). They die in hypoglycemia. At autopsy one finds that the labile fraction of liver protein has disappeared but there has been relatively little utilization of peripheral protein.

Likewise on fasting, the adrenalectomized animal is not able to utilize endogenous protein for the formation of carbohydrate and, as a consequence, dies from hypoglycemia. It is not only unable to mobilize endogenous protein outside the liver but it is unable to utilize fat from fat depots at a normal rate. Hepatic fat, however, seems to be available for energy (40), (Figure 4).

Apparently *pantothenic acid* in the rat is closely linked to adrenal function. One of the results of pantothenic acid deficiency in rats is adrenal hemorrhage and necrosis (41). Gaunt (42) found that in either pantothenic acid or riboflavin deficiency there was a decreased resistance to water intoxication. Resistance was restored by cortical hormones. Ralli (43, 44) has also shown a relationship between the failure of hair pigmentation in pantothenic acid deficiency and the adrenals. Adrenalectomy of rats on a pantothenate-deficient diet led to increased growth and repigmentation of the hair. Administration of desoxycorticosterone prevented repigmentation.

Whether protein intake affects the function of the adrenal cortex is open to dispute. Tepperman, Engel and Long (45) reported an en-

---

←

FIG. 3. Effect of estrogens on the thyroid glands of rats on a low iodine diet.

A. Thyroid of rat on low iodine diet.

B. Thyroid of rat on low iodine diet injected with thirty gamma estrone daily for 12 weeks.

C. Thyroid of rat on low iodine diet injected with 9.4 gamma diethylstilbestrol daily for 12 weeks.

D. Thyroid of rat on low iodine diet plus 2.44 gamma I_2 daily for 12 weeks.

(F. X. Gassner: M. S. thesis, Colorado A. and M. College.)

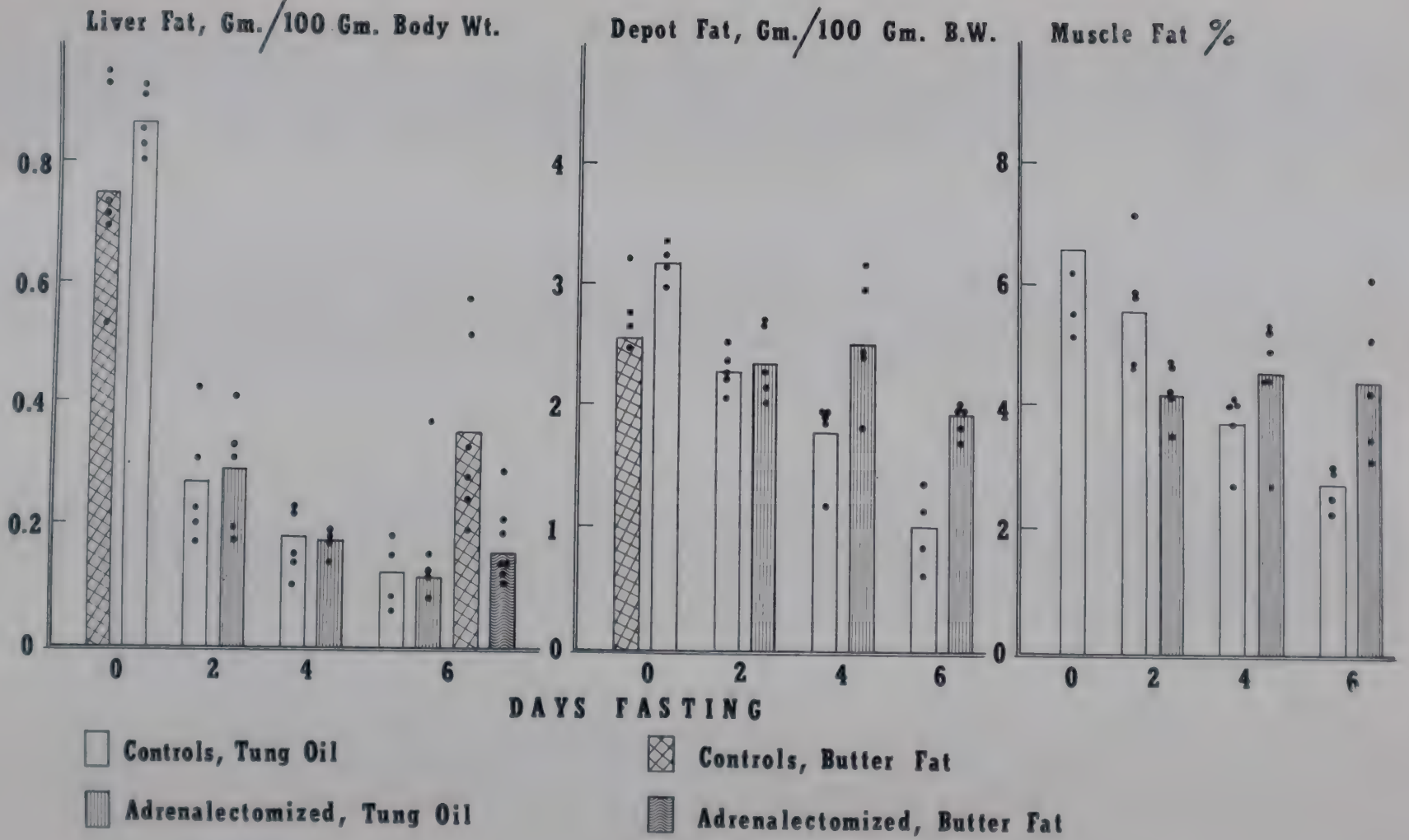


FIG. 4. Effect of fasting on the amount of liver, pararenal and gonadal depot, and muscle fat in normal and adrenalectomized male rats.

Each dot represents the analysis of a tissue from an individual rat. The height of the columns indicates the average value for the group.

largement of the adrenal cortex in young rats on three high protein diets. On the other hand Ingle (46), and Samuels, *et al.* (47) (using other sources of protein, and adult rats) found no effect. Benua and Howard (48) observed no influence in mice. The adrenal enlargement may depend on the age of the animals used. Again the difference in effect may be an indirect one caused by changes in ascorbic acid synthesis or utilization.

It seems well established that *ascorbic acid* is intimately involved in adrenal function. The ascorbic acid content of the adrenal cortex is

TABLE 5. EFFECT OF ADRENOTROPIC HORMONE ON CHOLESTEROL AND ASCORBIC ACID CONTENT OF ADRENALS OF 24-DAY-OLD RATS

Interval between administration of adrenotropic hormone (4 mg./100 g. body wt.) and removal of adrenals	Adrenal cholesterol		Adrenal ascorbic acid	
	No. rats	Mg. per 100 mg. fresh tissue	No. rats	Mg. per 100 g. fresh tissue
Controls	45	3.03±0.08*	8	314.2± 6.1
20 minutes	—	—	5	212.6± 6.1
1 hour	6	2.62±0.24	5	134.2± 6.9
3 hours	27	1.57±0.07	5	141.3±11.3
6 hours	8	1.71±0.08	5	237.0±15.2
9 hours	8	1.80±0.11	5	293.9± 6.1
12 hours	4	1.98±0.24	4	327.7±16.6
24 hours	7	3.06±0.19	2	351.4

* Mean and standard error.

(G. Sayers, M. A. Sayers, H. L. Lewis, and C. N. H. Long, *Proc. Soc. Exper. Biol. Med.*, 55: 238, 1944.)

very high; in fact it was from this source that the vitamin was first crystallized by Szent-Gyorgyi (49). Whenever there is an increased synthesis and release of cortical hormones due either to stress or to direct injection of adrenotrophic extracts, there is a rapid fall in ascorbic acid. Sayers (50) has used this fall in ascorbic acid as a means of exploring the adrenal-pituitary axis and as a method of assay for adrenotrophic and cortical hormones. Since cholesterol falls at the same time, although more slowly, it is inferred that ascorbic acid is involved in synthesis of cortical steroids from this source (Table 5).

The dependence of the adrenals on ascorbic acid in the diet cannot be readily demonstrated in those animals which synthesize most of

TABLE 6. ACETONURIA DURING EARLY DAYS OF FASTING IN NORMAL HUMANS

Subject	Fast No.	Height	Weight	Surface area	Acetonuria, gm. per sq. m.				
					Control	1st day	2nd day	3rd day	4th day
		in.	lbs.	sq. m.					
Female:									
R.B.	1	64	165	1.80	0.07	0.14	7.54	9.03	8.18
	2		157	1.77	0.02	0.07	3.03	10.84*	
	3‡		148	1.72	0.02	0.15	7.05		
G.C.D.	1	62	131	1.60	0.02	0.03	2.51	12.92	
	2		134	1.62	0.02	0.02	1.16	9.00	7.57
	3‡		140	1.64		0.05	3.04	9.62	
M.G.	1	57	100	1.35	0.00	2.17	4.47	4.96	7.30*
R.M.	1	66	124	1.63	0.05	0.34	4.03	6.11	6.24*
V.T.	1	64	147	1.71	0.01	2.49	5.45	9.43	6.60
	2		144	1.70	0.01	0.27	3.45	4.89	4.68
	3		147	1.71	0.00	0.21	4.96	7.89	5.32
Male:									
J.S.B.	1	70.5	150	1.86	0.04	0.04	0.05	0.28	0.37
	2		152	1.87		0.07	0.49	1.93	4.02
	3		154	1.88	0.00	0.00	0.27	2.16	3.30
H.J.D.	1	70.5	190	2.05	0.02	0.12	1.00	2.86	3.80
	2		186	2.04	0.02	0.14	2.46	3.95	4.38
	3		190	2.05	0.03	0.06	1.41	2.25	4.16
P.L.	1	68	148	1.80	0.04	0.04	0.52	1.12	2.39
	2		151	1.82	0.02	0.01	0.17	0.77	1.06
	3		157	1.84	0.01	0.03	0.27	0.71	0.90
P.W.S.	1	68	137	1.74	0.04	0.02	0.03	0.06	0.16
	2		142	1.77		0.02	1.01	0.69	1.97
	3		144	1.78	0.00	0.00	0.71	1.79	1.92
C.T.	1	70	240	2.26	0.04	0.02	0.27	0.70	1.86
	2		240	2.26	0.01	0.10	0.81	4.60†	3.34†
	3		240	2.26	0.00	0.02	0.23	0.57	2.15

* Estimated from eight-hour period.
‡ Menstruation just preceding or during period of fast.
† Hard manual labor during this experiment.
(H. J. Deuel, Jr. and M. Gulick, *J. Biol. Chem.*, 96: 25, 1932.)

this compound. Only the guinea pig, monkeys, and man are readily available species which require this vitamin. No studies have been directed toward this problem in man, but in the guinea pig the ascorbic acid of the adrenal falls on a scorbutic diet, and at the same time the ability to resist stress decreases. The same is probably true in man. The effect of ascorbic acid in the diet on the regeneration of cortical tissue should be studied.

Since certain phases of protein metabolism appear to require ascorbic acid (52), it may be that the effects of high protein diet on the adrenals is dependent on its influence on the availability of ascorbic acid, particularly in the young animal. Unless ample ascorbic acid is supplied, the premature infant shows the same disturbances in amino acid metabolism which are seen in the scorbutic guinea pig (53).

Gonadal Hormones

The gonadal hormones have definite effects on the disposition of foodstuffs. The estrogens exert their influence largely on the balance between carbohydrate and fats. Deuel and co-workers (54) demonstrated that female rats and humans have an increased tendency towards ketosis on any ketogenic diet or during fasting. The effect of fasting in humans is well illustrated in Table 6 taken from their data. This was accompanied by a greater accumulation of fat in the livers (55). Ovariectomy eliminated this tendency and produced a nutritional balance resembling that of castrate or normal males. Ingle (56) has been able to produce diabetes in the normal rat by injection of large doses of estrogen. He has shown that this is a direct effect on carbohydrate metabolism because he was able to get a similar result in hypophysectomized adrenalectomized rats which were maintained with constant doses of pituitary and adrenal extract (57). The mechanism by which estrogens increase fat metabolism and decrease carbohydrate utilization has, as yet, not been determined.

The estrogens also affect deposition of bone. Gardner *et al.* (58) have shown that administration of large doses of these hormones may cause almost complete calcification of marrow cavities of the long bones. The force required to break such bones is compared with that for untreated animals in Figure 5. The calcium balance becomes

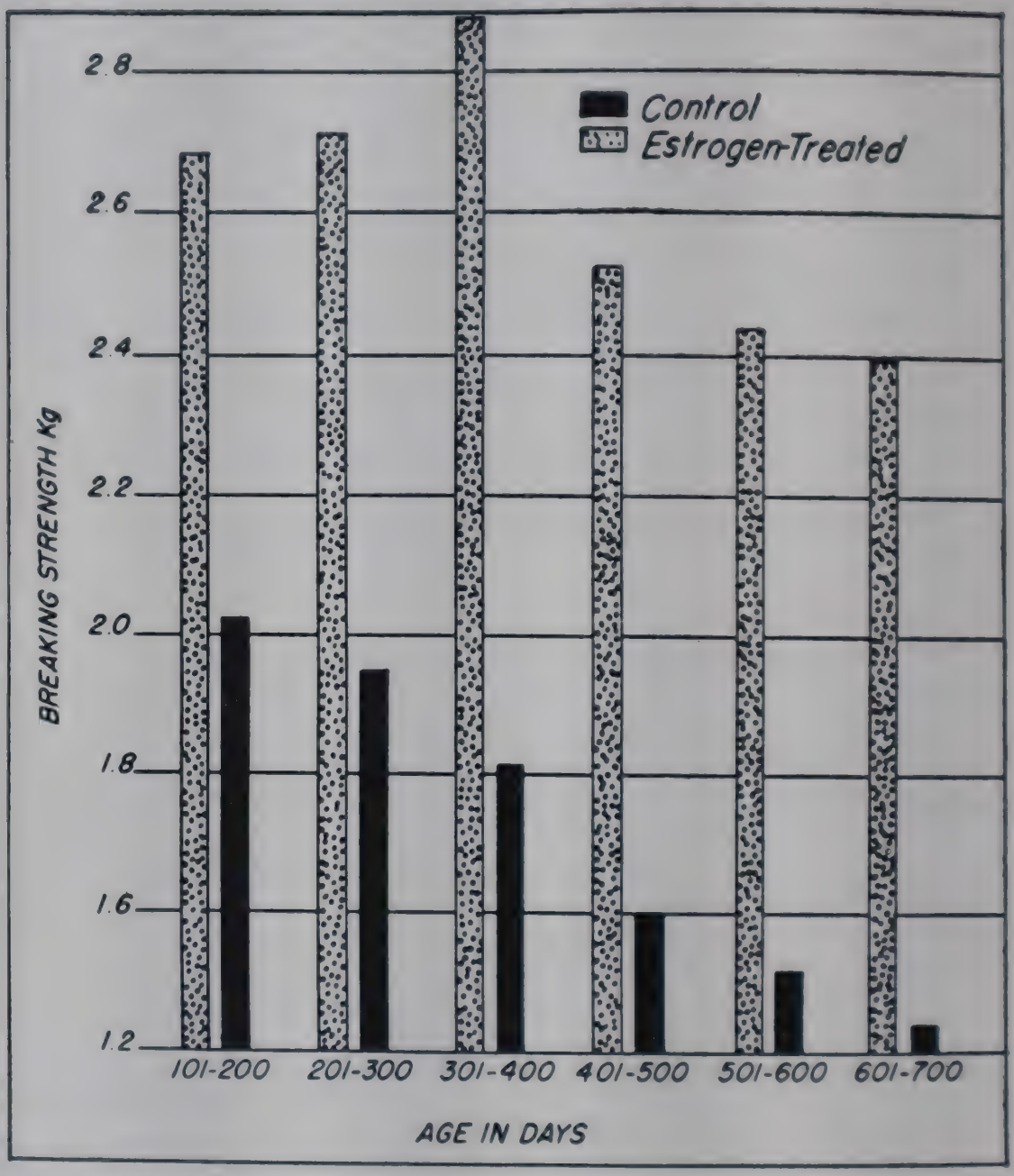


FIG. 5. Average "breaking strength" of the femurs of the hybrid male and female mice of the estrogen-treated and control groups at different ages.

(W. U. Gardner: *Endocrinology, 32*:149, 1943.)

positive. Progesterone appears to offset this tendency to calcification both in rats given estrogens and in normal animals (59).

The estrogens are related to vitamin needs, but in different ways in various species. Hertz, Fraps and Sebrell (60) have found that the action of estrogens plus progesterone on the avian oviduct induces the formation of avidin, the protein which combines with biotin and prevents its absorption from the intestinal tract.

When Ershoff and Deuel (61) fed alpha-estradiol at a level of five mg. per kilogram of diet, there was a reduction in body weight and gonad weight if the diets contained the usually known synthetic vitamins of the B complex in either normal or increased amount. When such animals had yeast added to their diets, however, normal growth and normal development of the gonads was maintained. This would indicate that one of the less well-defined factors is capable of offsetting the detrimental effects of the estrogen.

A direct influence of folic acid on the response of the oviduct of birds to the injection of estrogens has been demonstrated by Hertz (62). Apparently the relationship in rats is not so marked. Deficiencies of pantothenic acid, riboflavin or pyridoxine did not apparently affect the response of the oviduct despite the accompanying effect on growth.

While pantothenic acid showed no disturbance in the oviduct response of the chicken, Nelson and Evans (63) found that this vitamin is necessary for implantation and intra-uterine development in rats. Niacin had no influence on pregnancy.

The rôle of vitamin A in the estrous cycle has been disputed. When deficiency is produced, keratinization of epithelial cells occurs in all parts of the body, and the uterus and vagina are not immune. The vaginal smear from such an animal will resemble that of continuous estrus. Richter (64) has found, however, that the variations in activity coinciding with the estrous cycle still occur at four to five day intervals and the ovaries appear to follow a normal course. The most probable explanation is that the gonadal hormones are produced in their proper order but they cannot act normally on the keratinized epithelium of the deficient individual.

Sherwood (65) has claimed that excessive vitamin A interfered with the normal cornification of the vagina following endogenous or exogenous estrogen, but three other groups of workers have been unable to find any untoward effects of excess vitamin A on the gonads (66, 67, 68). It seems doubtful that any significant damage to human beings could be done by administration of vitamin A in the ordinary dosage used.

Ascorbic acid also seems to be specifically involved in the reactions of the genital system. As in the case of the adrenals, where its rela-

FIG. 6. A. Ovariectomised rat injected with eight gamma oestradiol benzoate-butyrate three times only during first week of experiment. Lumen without mucosal foldings, high epithelium. Approximately in middle of section, squamous metaplasia in four mucosal glands, in two on left of uterine lumen completely, and in the others (right of uterine lumen) partially closing the lumen of the glands. Rat 256 g., uterus 153 mg.

B. Ovariectomised rat injected during first week with oestradiol benzoate-butyrate (as in Figure 1) and during four following weeks with two mg. progesterone daily six times a week. Typical progestational changes—foldings of mucosa, low columnar epithelium, uneven enlarged lumen. Rat 260 g., uterus 203 mg.

C. Ovariectomised rat injected with oestradiol benzoate-butyrate as in Figure 1, but receiving during four following weeks vitamins B and C. The foldings of the mucosa

tion to hormone metabolism is established, ascorbic acid is particularly high in the corpus luteum (69). It seems to be low in other ovarian structures and in follicular fluid. It increases in concentration during the development of the corpus luteum and decreases during regression (70).

The effect of ascorbic acid on progestational phenomena is not simply on formation of progesterone, however. Saffrey and Finerty (71) confirmed the findings of Ingier (72) that pregnant guinea pigs maintained on a low ascorbic acid diet aborted or resorbed the embryos. Injection of corpus luteum extract did not prolong gestation but addition of the vitamin would. This can be correlated with the observations of Israel and Meranze (73) and Korenchevsky and Hall (74). Both groups primed ovariectomized animals (rabbits, rats and mice) with estrogens while on a normal diet. The animals were then injected with additional amounts of ascorbic acid. The endometrium became enfolded and the lumen of the uterus enlarged as with progesterone. Korenchevsky and Hall, however, call attention to the fact that the epithelial cells were still the tall columnar type seen after estrogen stimulation (Figure 6). The change was not completely to the secretory type. It seems, therefore, that ascorbic acid plays a rôle in both the function of the corpus luteum and in the nutrition of the uterus but is not a substitute for a hormone.

The high content of ascorbic acid in the corpus luteum led to some trials of the vitamin in habitual abortion. Ley (75) reported success in ten women but further studies have not borne out the original hopes. The same is true regarding the rôle of progesterone itself in habitual abortion. Apparently there are multiple causes of this condition: a few patients may be benefited by ascorbic acid, a few by progesterone; but one cannot count very much on these factors.

Thus far, we have largely discussed the abnormalities produced

---

and the lumen as in Figure 2, but the epithelium is high as in Figure 1. Rat 245 g., uterus 248 mg.

D. Another ovariectomised rat treated as in fig. 3 Similar picture, but lumen like that in Figure 1. Rat 210 g., uterus 200 mg.

The effect of ascorbic acid on the uterus of rabbits treated with estrogens.

(V. Korenchevsky and K. Hall, *J. Path. & Bact.*, 57:141, 1945.)

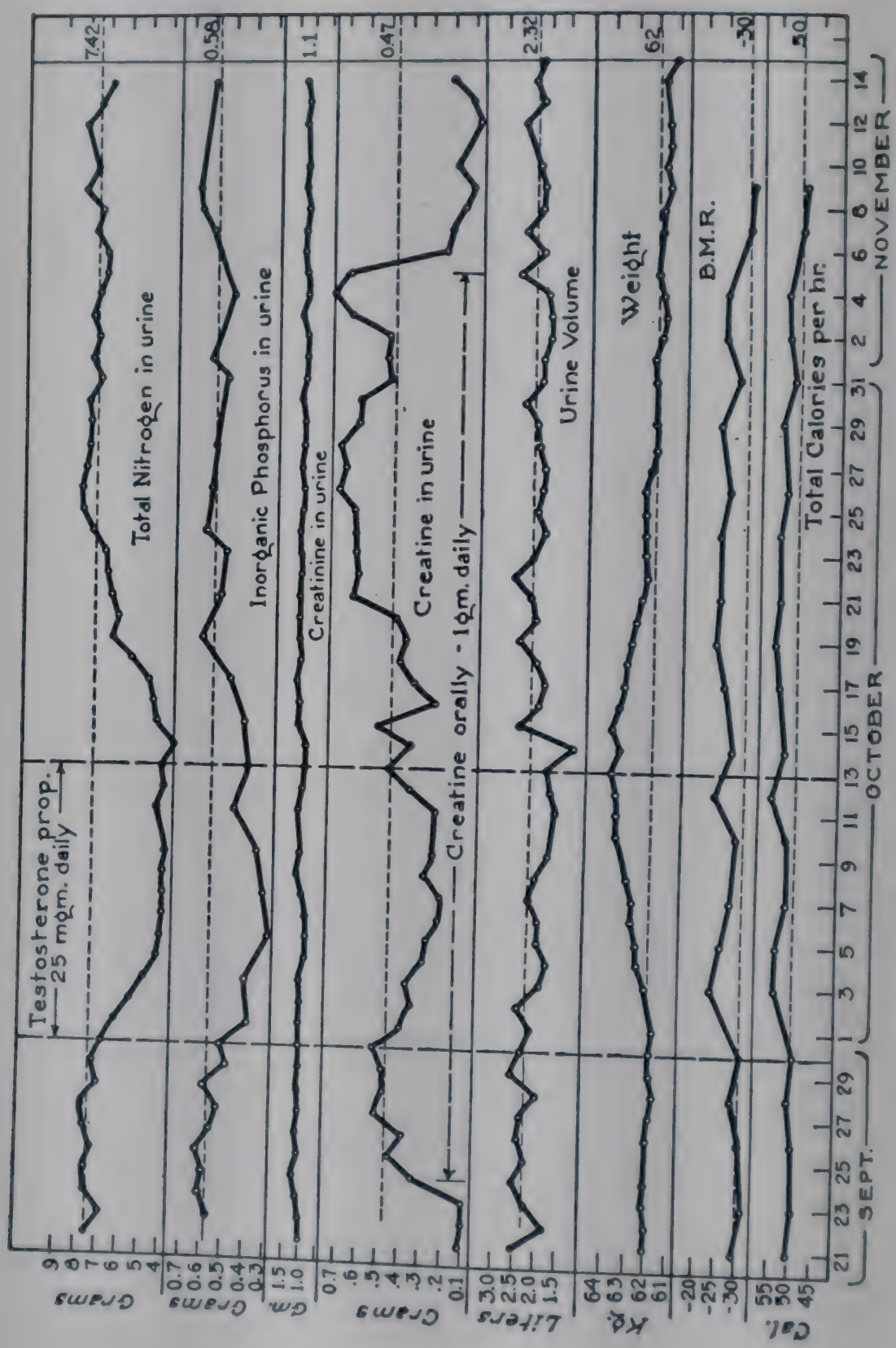


FIG. 7. The effect of intramuscular injections of testosterone propionate on the excretion of several urinary constituents, body weight and BMR of the eunuchoid J.X.

(A. T. Kenyon, K. Knowlton, I. Sandiford, F. C. Koch, and G. Lotwin: *Endocrinology*, 26:26, 1940.)

by undernutrition. There is one type of hormonal disturbance which results when *caloric intake has been excessive.* In obese women one often observes irregular menstrual cycles. This would appear to be due to the leveling influence of the fat stores on the circulating estrogens. We have investigated the estrogenic content of the abdominal fat of obese patients and found significant amounts of these substances. Since they are so readily soluble in lipids, the cause of the irregularity in cycles probably is the tendency of the fat stores to take up the estrogens when they are at a high concentration in the blood. Conversely they permit their diffusion, when the estrogen level in the circulating fluids is low. Thus the normal fluctuation would be ironed out and the changes in the uterus and the vagina, therefore, affected.

The major effect of the androgens is to increase *protein anabolism.* The storage of water, potassium, phosphorus, and creatine is also increased (76), (Figure 7). This indicates that the protein is laid down in the body in the form of muscle tissue or some tissue which closely resembles it in composition. Positive nitrogen balances are most easily and markedly produced in eunuchoid individuals or those suffering from pituitary deficiency; however, positive balances have been produced in normal adult males and females on adequate diets (77). Even in conditions of undernourishment, the negative balance is reduced by administration of androgens. The increased protein anabolism is associated with decreased urea levels in the blood and a fall in urine nitrogen. This would indicate that there is a decreased deamination.

The protein which is formed apparently exists in two forms, or at least passes through two stages. If the androgen has been administered for only a few days, most of the stored nitrogen escapes on cessation of androgen administration. If, however, the androgen has been administered for ten days or more, a considerable portion of the stored nitrogen remains after cessation of treatment with the hormone. It may be that the protein first formed is in a relatively labile state but is gradually transformed into more stable structures.

The effect of androgens on the need for the various vitamins has not been well worked out. One would expect that the need for

pyridoxine would be increased, since it plays a considerable rôle in protein metabolism. This field needs further exploration.

Besides the direct effects of nutrition on production or those on the end organ, there are effects on the destruction of the steroid hormones. The normal state is the result of a dynamic balance between production, destruction, and excretion of these substances. The inactivation processes involved require certain nutrients and a deficiency of these may lead to increased endocrine effects.

The most important organ in the inactivation of the steroid hormones appears to be *the liver*. Zondek (78) first showed that the liver destroyed estrogenic activity. He not only showed that incubation with liver tissue would inactivate estrogens, but he claimed to be able to do it with cell-free solutions and with a resuspension of powdered desiccated liver tissue (79). Talbot (80) showed that inhalations of carbon tetrachloride which would produce functional liver damage would also decrease the inactivation of estrogens.

Biskind (81) found that rats on diets deficient in the B complex failed to metabolize estrone or estradiol. Segaloff (82) and Unna (83) found that a thiamine or riboflavin deficiency interfered with inactivation, but deficiency of the other members of the B complex which they tested had no effect. The specificity of this relation of thiamine and riboflavin has been recently brought into question by Drill (84), who found that animals paired-fed but with abundant vitamins, lost the power to destroy estrogens as readily as the thiamine-deficient rats. The explanation for this observation may be in the experiments of Gyorgy (85) who found that dietary liver damage produced by a low protein-high fat diet prevented estrogen inactivation, and that administration of lipotrophic factors such as methionine would restore the destructive ability. It may be that the severe limitation of food intake on thiamine deficiency may produce deficiency of lipotrophic amino acids.

Evidence of the impairment of estrogen metabolism in human beings with liver damage has been cited by Glass and co-workers (86).

Testosterone destruction in the presence of dietary deficiency has been studied by Biskind (87). He found no evidence of impaired destruction in vitamin B deficiency as he had with the estrogens. Vitamin B deficiency would, therefore, disturb the estrogen-androgen

balance. He then investigated the relation of nutritional deficiency to menstrual disturbances (115) and to male infertility (116). In a number of patients there was a history of dietary deficiency, and the symptoms were relieved by vitamin therapy. Menstrual irregularities are also common among undernourished populations (100).

The problem of the effect of dietary cirrhosis or fatty degeneration

TABLE 7. STEROID HORMONES DESTROYED BY LIVER MINCE WHEN INCUBATED AEROBICALLY AT 38° C. FOR ONE HOUR

Hormone	Amount mg.	Liver tissue gm.	Treatment	Amt. of hormone recovered mg.	Amt. of hormone destroyed mg./gm liver/hr.
Testosterone	.200	.660	Live	.145	.084
Testosterone	.200	.675	Boiled	.213	
Testosterone	.400	.545	Live	.286	.209
Testosterone	.400	.735	Boiled	.403	
Testosterone	.400	.800	Boiled	.398	
Methyl testosterone	.200	.560	Live	.149	.092
Methyl testosterone	.200	.740	Live	.126	.100
Methyl testosterone	.200	.635	Boiled	.197	
H_2O soluble testosterone diethyl aminoethyl carbonate	.300	.580	Live	.054	.424
H_2O soluble testosterone diethyl aminoethyl carbonate	.300	.515	Live	.054	.478
H_2O soluble testosterone diethyl aminoethyl carbonate	.300	.610	Boiled	.289	
Progesterone	.200	.630	Live	.134	.106
Progesterone	.200	.685	Live	.149	.074
Progesterone	.200	.755	Boiled	.213	
Progesterone	.200	.865	Boiled	.197	

(Samuels and McCaulay.)

has not been studied, however, in animals. Samuels *et al.* (88) have found that human cirrhotic livers do not destroy testosterone so rapidly as normal livers; in severe cirrhosis, destruction may be nil.

Burrill and Greene (89) have described experiments which indicate that the androgens originating in the adrenal cortex are not so readily destroyed by the liver as are the testicular androgens. Since the observations are based on a comparison of adrenal implants in the mesentery with implantation of testosterone pellets in the same region, the question of how much androgen was produced by the adrenal

implants cannot be answered. It may be that this was greater than the amount of testosterone absorbed from the pellets. More direct evidence must be obtained before this conclusion can be considered proved.

Progesterone (90) and the adrenal steroids (91) are apparently metabolized by the liver. In fact, there is good reason to think that any steroid with an alpha-beta unsaturated ketone group in ring A will be attacked (92), (Table 7). Since this includes all of the most active steroid hormones except the estrogens already discussed, the turnover must be great. Nutritional effects on the liver should be expected to influence the various functions dependent on steroid metabolism.

Anterior Hypophysis

The foregoing discussion of the relation between nutrition and endocrine glands which are under the control of the hypophysis indicates the manifold effects which this organ may have on nutritive processes through its trophic hormones. In addition there are certain direct effects. One of the most marked is the effect of the so-called *growth hormone*. If the pituitary gland is removed from a growing animal, growth ceases. If the animal is an adult, there is a loss of weight associated with decreased appetite.

If such animals are given the normal amount of foodstuffs by stomach tube, however, weight can be maintained or increased; the primary defect is not inabsorption. In the animal hypophysectomized during the growing period, very small positive nitrogen balances can be maintained but practically all of the food above that required for energy in either the growing or the adult animal is stored as fat (see Table 1), (5, 93). This is true even though the amount of protein fed may be quite large. Such animals, therefore, can assimilate protein, deaminate it, and convert it to fat, but they cannot synthesize it to any extent into new tissue. The loss of weight in the animal eating *ad libitum* is due to depressed hunger apparently associated with decreased protein synthesis.

There is some protein synthesis possible in such hypophysectomized animals, however. If such animals are operated upon, the wounds heal rather readily. If areas of the skin are shaved, the hair grows

back, although more slowly than normal. The laying down of new tissue, therefore, is retarded much more than the replacement of tissue previously formed.

If some disturbance of hunger balance results, such as damage to the hypothalamus, then the hypophysectomized animal will become more obese than a normal animal with the same damage, since the normal animal will not only lay down fat but will use some of the excess food for increased tissue function. In the hypophysectomized animal, it is converted entirely into fat, thus resulting in the typical Frohlich's syndrome.

Highly purified preparations of the growth hormone have been shown to reverse this picture in hypophysectomized animals. Not only will it cause formation of protein on the ordinary food intake, but Marx, Herring and Evans (94) showed that it would cause storage of nitrogen in fasted, hypophysectomized rats; the hypoglycemia of such animals would be accentuated and typical hypoglycemic convulsions would be produced. Evans (95) was among the first to demonstrate that injections of pituitary growth extracts would produce giants if the epiphyses of the long bones were not united. When union had occurred, acromegalic animals resulted.

Apparently the growth hormone is not the sole factor involved in this synthesis, however; there seems to be a synergism with insulin. Evans and his co-workers (96) found that injections of highly purified growth hormone into fed, partially depancreatized rats increased the output of glucose in the urine. This effect has been observed by Mirsky (97) and Gaebler and Robinson (98) with crude growth extracts. These workers also found an increase in nitrogen excretion in depancreatized animals rather than nitrogen storage. It would seem, therefore, that the anabolic effect of the growth extract requires the associated action of insulin. There is reason to think that other factors may also be involved for maximal anabolism.

The growth hormone also affects the compounds available for catabolic processes and, therefore, nutritional needs. Since more amino acids are being formed into protein, less are available for catabolism. Less methionine is available for methylation, and the intake must be increased to compensate for this. Amino acids are not being broken down so much into carbohydrate and the supply of

energy must be made up. This need for additional sources of energy is brought out by the observations previously mentioned of hypoglycemic convulsions in animals with pituitary deficiency when purified growth hormone was injected.

Since the need for many vitamins is greater during the period of natural growth than during adult life, it is not surprising that the need for these is also increased during administration of the growth

TABLE 8. THE EFFECT OF GROWTH HORMONE ADMINISTERED WITH OR WITHOUT VITAMIN A ON GROWTH AND ON SURVIVAL TIME OF RATS ON A VITAMIN A-FREE DIET

Group No.	Number of rats		Supplements given daily*		Values at end of depletion period		Final weight	Per cent surviving
	Males	Females	Vitamin A	Growth hormone	Average age	Average wt.		
			I.U.	rat units	days	gm.	gm.	
1	4	4	0	0.0†	49.1	93.6	81.6	62.5
2	3	3	0	2.5	46.5	87.8	86.5	33.3
3	7	4	0	25.0	49.2	91.2		0.0
4	3	3	10	0.0†	48.2	91.2	151.3	100.0
5	3	3	10	25.0	47.5	83.4	164.7	100.0

* Supplements started after vitamin A depletion (Assay period only).
† Received injections of placebo intraperitoneally daily.
(B. H. Ershoff and H. J. Deuel, Jr., *Endocrinology* 36: 280, 1945.)

hormone. Ershoff and Deuel (99) found that administration of growth-promoting extracts of the anterior pituitary gland to rats on a vitamin A-deficient diet precipitated acute symptoms earlier and shortened survival. The data are given in Table 8. The need for vitamin D must also be significantly increased with the accelerated bone growth. The skeletons of acromegalic giants often show many of the typical rachitic changes.

Both Margitay-Becht and Wallner (101) and Ershoff and Deuel (99) were unable to obtain any evidence of growth effect in animals deficient in vitamin A. That there was some effect of the hormone in the animals of the latter workers is shown by the early precipitation of symptoms and death previously mentioned. It may be that the growth hormone exerted an anabolic effect involving vitamin A, but that the supplies of the latter were so limited and so soon ex-

hausted that the results of hormone action on weight did not exceed the experimental error.

This interrelation of the growth hormone and the vitamins is not surprising since many of the latter are parts of enzyme systems involved in cellular metabolism. The ability of growth hormone preparations to precipitate vitamin deficiencies at an earlier time, as well as the importance of the latter in the action of the hormone, can be used as a means of determining those coenzyme systems which are, directly or indirectly, involved in anabolism.

There would also seem to be a definite diabetogenic factor in the pituitary extracts. Houssay (102) was the first worker to point out the great reduction in pancreatic diabetes if the pituitary gland were removed. He also demonstrated that injections of crude pituitary extract would increase the diabetes of the depancreatized normal animals or precipitate it in depancreatized-hypophysectomized preparations. He showed that temporary diabetes could be produced in normal dogs. Young (103), by administering large and increasing doses of crude pituitary extracts to dogs, was able to produce diabetes which continued after cessation of the extract. In these animals the islet tissue of the pancreas had been permanently damaged, apparently by over-stimulation and exhaustion. Recently, Cori (7) has been able to show that a diabetogenic extract of the pituitary gland would inhibit the enzymic conversion of glucose to glucose-6-phosphate by hexokinase in simple noncellular systems (see Figure 1). This was the first effect of the hormone to be demonstrated in isolated enzymic reactions. The exact rôle the diabetogenic factor plays in normal metabolism and nutrition is yet to be determined.

Now let us turn to the other side of the picture. History shows that there is *a depression of fertility* as well as *an influence on growth* when human populations are subject for considerable periods of time to conditions of undernutrition. The effects of undernutrition on the endocrine system of humans have been particularly observable in Europe during the war years. Here the results could be compared with adequate data on the population when the majority were reasonably well fed, an impossibility in Asia. Menstrual irregularities were much more frequent and fertility was reduced (100).

The growth of children, as measured by increase in height, was also reduced (117, 118), (Figure 8).

Tauber describes the appearance of a group of 496 undernourished children from the Netherlands thus: "The children were mostly between seven and fifteen years of age; three were sixteen years old. On arrival they presented a somewhat different picture from that ex-

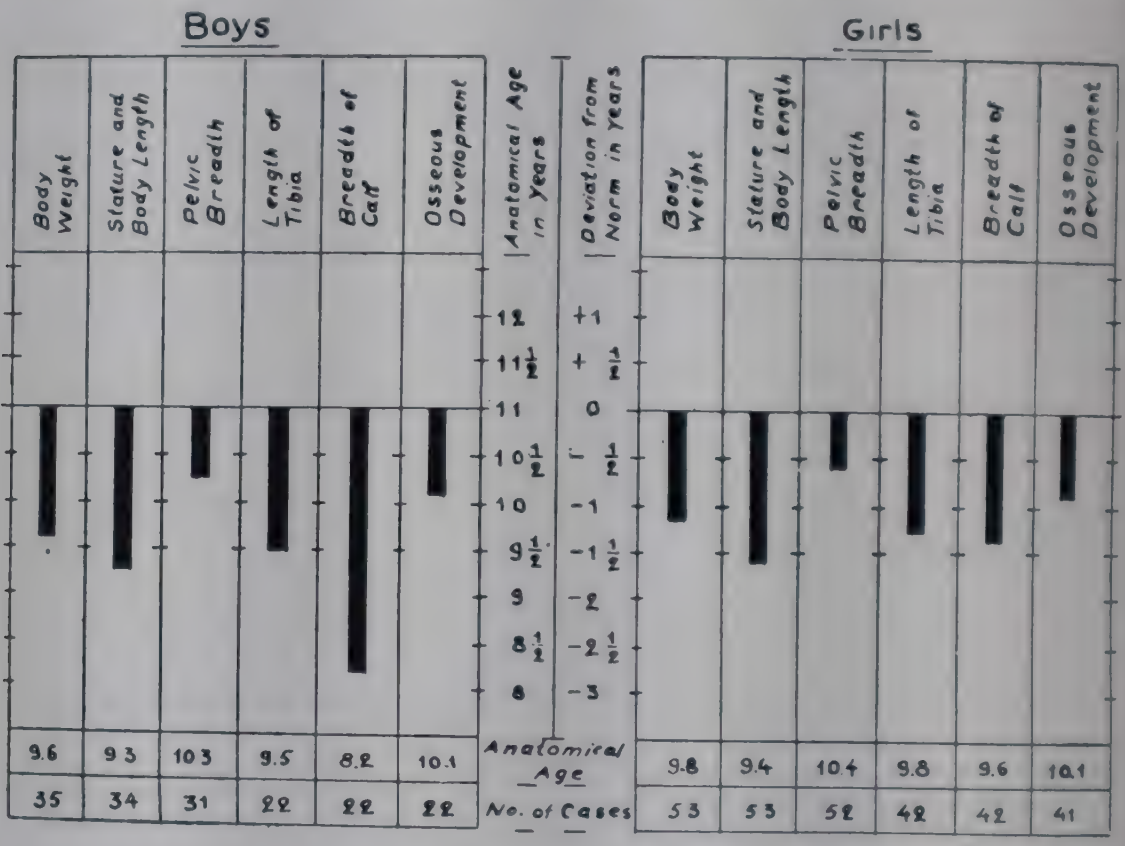


FIG. 8. Anatomical ages based upon body measurements and osseous development of 11-year-old children in Marseilles in the fall of 1942.
(H. C. Stuart, *J. Pediat., 25*:262, 1944.)

pected. The main feature of the malnutrition was not so much wasting as the general undersize. Pallor was notable and many children were rather weak. The apparent age of many children was well below the actual age."

This decrease in growth and in gonadal activity are both compensatory changes which help the organism to survive in regions of limited food supply. Jackson (104) has studied the effect of caloric restrictions in great detail, both in the rat and in the human being. In the growing rat, Jackson found that caloric restriction to an extent which

would maintain the animal but not permit increase in weight would stop the development of the ovaries, testes and secondary sex organs. The ovaries were the most sensitive. In adult animals mild caloric restriction soon caused cessation of estrous cycles in the females, and somewhat greater restriction for a longer period of time caused atrophy of the secondary sex organs in the male. If the animals were re-fed, they would recover normal function and growth completely providing the period of partial inanition had not been too long. After prolonged undernutrition even to a mild degree, there was permanent interference with both gonadal function and growth. This was particularly true if the period of restricted food intake was during the pubertal period. Similar changes were noted by him in undernourished children.

Experimental work in the last 15 years indicates that the depression of the pituitary gland is a primary cause of these changes. Mason and Wolfe (105) in 1930 showed that the pituitary glands of female animals which had been starved had less gonadotrophic activity. In 1931 Moore and Samuels (106) found that the atrophy of the secondary sex glands in the male rat on thiamine-deficient diets was due primarily to depressed pituitary function. As shown in Table 9, if pituitary gonadotrophic extracts were injected in such animals, normal testes and secondary sex organs could be maintained even though the animal died of the deficiency. They also demonstrated that it was not the thiamine deficiency which was the primary cause of the atrophy. If rats receiving adequate amounts of all vitamins were restricted to the caloric intake of the thiamine-deficient animals, the male sex organs underwent the same atrophy. Again they could be restored without changing caloric intake if the gonadotrophic extracts were administered.

The gonadotrophic activity of the pituitary glands of female rats is even more sensitive to undernutrition. Drill and Burill (107) repeated the experiments of Moore and Samuels using female rats and obtained similar results. Inanition, similar to that in thiamine-deficient animals, in rats receiving adequate vitamins produced the same reduction in ovarian activity and cessation of estrous cycles. Injection of gonadotrophic extracts would bring about the develop-

TABLE 9. EFFECT OF TESTOSTERONE AND HYPOPHYSEAL GONADOTROPHIC EXTRACT ON THE ATROPHY OF THE MALE SEX ORGANS IN THE RAT ON A THIAMINE-DEFICIENT DIET

Animal	No. days on diet	Body weight			Seminal vesicles at first operation	Days of injection	Condition at end		
		Initial	Per cent change at first operation	Per cent change at end			Testis	Prostate	Seminal vesicle
A. Thiamine-deficient diet, no hormone									
206	61	259		−47			4−	3−	0
211	70	190		−34			4	3−	0
212	70	196		−46			4−	2	0
210	73	256		−53			4	2	0
B. Fifty per cent thiamine requirement added to diet, no hormone									
221	70	54		+155			4−	4−	3
222	70	53		+155			4−	4−	4−
C. Inanition plus excessive thiamine requirements, no hormone									
220	24	220		−23			4	4−	3
228	33	210		−40			3	1	0
229	33	231		−41			4−	1	0
230	33	331		−33			4−	1	0
D. Thiamine-deficient diet plus testosterone									
280	24	179	−23	−34.5	0	10	4−	4	4−
279	24	189	−28	−44.9	4−	10	4−	—	4−
247	32	226	−27	−30.5	0	11	4−	4	4
248	32	218	−26	−30.9	0	11	3	4−	4
E. Thiamine-deficient diet plus hypophysis extract injection									
281	24	187	−28	−36.4	0	10	4−	4	4
282	24	216	−23	−34.5	0	10	3	4	4
246	32	212	−36	−45.5	1	10	4−	4	4
284	36	211	−28	−45.0	0	10	4−	4	4

(C. R. Moore and L. T. Samuels, *Am. J. Physiol.* 96: 278, 1931.)

In series D and E, rats were placed on a thiamine-deficient diet until they had lost approximately thirty per cent of their original body weight. One seminal vesicle was then removed for grading and the rats were continued on the deficient diet for 10–11 days, the specified hormone being injected throughout this latter period. Testes, prostate and seminal vesicles were then removed and graded.

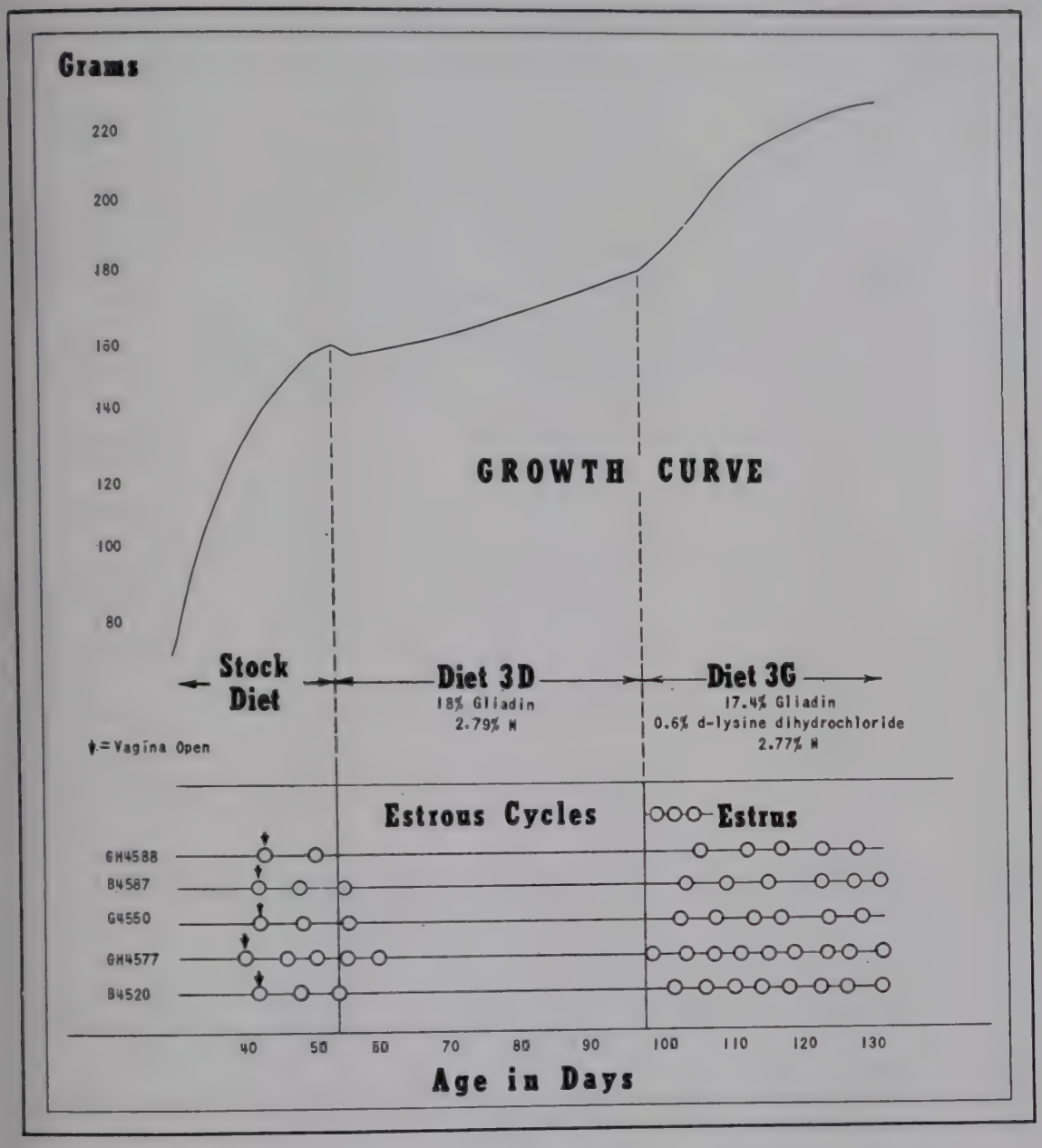


FIG. 9. The effect of adding 0.6 per cent of d-lysine dihydrochloride to a diet containing gliadin as the sole source of protein. Estrus is indicated by a circle. (P. B. Pearson: *Am. J. Physiol., 118:* 786, 1937.)

ment of these ovaries and restoration of estrus even though the inanition was maintained. Guilbert and Goss (108) demonstrated that proteins could be a limiting factor. When female rats were fed diets containing less than seven per cent of protein, estrus cycles became irregular and finally ceased in most animals, even though the normal total caloric intake was maintained. If the protein content of the diet was seven per cent or greater, no irregularity in the

estrous cycles resulted. The work of Pearson (109) would indicate that lysine might be the limiting amino acid in maintaining ovarian function. Figure 9 illustrates the result of lysine deficiency and subsequent supplementation.

While protein is a factor in pituitary gonadotrophic activity, it is not the only factor. We have just completed a series of experiments in which the animals received their entire caloric ration as protein, but in which the caloric intake was not sufficient to maintain weight. Approximately twenty per cent of the body weight was lost in five

TABLE 10

Diet Cal./100 sq. cm./day		Change in body weight per cent	Wt. seminal vesicles gm.	Wt. prostate gm.
Protein	Fat			
2.5	10	− 9	.314	.313
1	13	+ 3	.097	.135
11	1	−22	.120	.165

weeks. These animals were compared with rats receiving much less protein but a total caloric intake sufficient to just maintain their adult body weight. The pertinent data are given in Table 10. In the first group, in spite of the fact that they received more protein than the second, there was severe atrophy of the secondary sex organs. In the second group these tissues functioned normally. It would seem then that it is necessary to have both adequate protein and a total caloric intake which will satisfy the needs of the body without drawing upon endogenous protein sources. In other words, if the diet is not sufficient in calories, the protein, both of the food and the tissues, is rapidly used for energy and the pituitary gland is not able to obtain sufficient material for synthesis of the protein hormones.

The work thus far cited has largely been done on animals. This is because in the animal the experimental conditions can be controlled and the particular organs responsible for the disturbance can be obtained. *All of these facts once established can be paralleled by human cases.* The importance, therefore, of recognizing the influence of

hunger and malnutrition on the endocrine system must be borne in mind by the medical profession.

Particularly significant is the greater susceptibility of the pituitary gland to damage *at the time of puberty.* It is at this time that the damage may more easily become permanent. This was well illustrated in two recent cases at the Salt Lake County General Hospital. They were women in which diabetes had been recognized at the ages of 11 and 13 years. Severe diet restrictions were instituted and both had given evidence of undernourishment during the subsequent four or five years. In one woman proper dietary measures were begun at the age of 17, at which time she had not menstruated. Thereafter, with insulin and adequate total caloric intake, she gained in weight but did not menstruate until the age of 22. Since then she has had bleeding periods about once a year, but normal function has never returned. In the other case menstruation also did not begin until restoration of an adequate caloric intake with proper insulin control. She began to menstruate at the age of 18, one year after restoration of adequate nutrition. She also has been very irregular, bleeding periods being quite far apart. The vagina and uterus are infantile, the latter organ being so small as to be hardly palpable. She has also remained a dwarf, being less than five feet tall, although her growth during her earlier years was entirely normal. The mammary glands never developed. Undoubtedly, this condition of malnutrition would probably account for many of the dwarfisms and other disturbances in diabetic children as they pass through puberty. It seems, therefore, very important that nutrition be controlled during pubertal development if permanent gonadal damage is to be avoided.

The effect of undernutrition on the pituitary gland is not limited to the gonadotrophic hormones, though these apparently are most sensitive to nutritional deficiencies. Mulinos and Pomerantz (110) have shown that growth, thyroid and adrenotrophic activity can be disturbed. The human case last quoted, as well as the observations on European children previously noted, illustrates disturbances of growth similar to those seen in the studies of Jackson in rats. Mulinos and Pomerantz demonstrated that growth extracts from the pituitary gland would restore the increase in length of the skeleton even though the total weight might be constant.

They also observed that while the adrenals of severely restricted animals would show an hypertrophy, partially undernourished rats which would outlive those on the severe deficiencies showed adrenal atrophy. Here again, pituitary extracts would restore the adrenal gland (111). Selye (112) at first was unable to confirm this on chronic, mild undernutrition. However, he found that when a high carbohydrate diet was fed so that not only was the caloric intake restricted but the protein intake was considerably reduced, he obtained the adrenal atrophy observed by Mulinos and Pomerantz. It seems, therefore, that while the adrenotrophic hormone may be formed at lower nutritional levels than the gonadotrophins, it also is limited by caloric and protein intake.

Summary

In summary, then, let me emphasize first that endocrine factors are important in determining the caloric need and the methods by which foods will be utilized in the animal body. Their effects are often offset in part by compensatory adjustments of the hunger mechanism. The compensatory adjustments, however, may not be perfect; they may be too great or too little and abnormalities, therefore, result.

In particular, the pituitary growth hormone is essential for protein anabolism. In its absence, anabolic processes will not go on no matter what the intake of protein is. The growth hormone will act much more efficiently if adequate thyroid, gonadal, and insulin levels are also maintained.

Nutrition, in turn, will effect hormone production. This also can be observed in human beings and is particularly important during the period of puberty. The pituitary hormones seem most sensitive to deficiencies either in caloric intake or adequate protein. The other endocrine organs may also be disturbed by specific deficiencies. An example is the adrenal gland and pantothenic acid restriction. These matters should always be kept in mind in dealing with human beings who show signs of endocrine disturbance.

BIBLIOGRAPHY

1. Smith, P. E.: The disabilities caused by hypophysectomy and their repair; The tuberal (hypothalamic) syndrome in the rat, *J.A.M.A., 88:*158, 1927.
2. Brobeck, J. R., J. Tepperman, and C. N. H. Long: Experimental hypothalamic hyperphagia in the albino rat. *Yale J. Biol. Med., 15:*831, 1943.
3. Tepperman, J., J. R. Brobeck, and C. N. H. Long: The effects of hypothalamic hyperphagia and of alterations in feeding habits on the metabolism of the albino rat. *Yale J. Biol. Med., 15:*855, 1943.
4. Anderson, A. S., and L. T. Samuels: Unpublished work.
5. Samuels, L. T., R. M. Reinecke, and K. L. Bauman: Growth and metabolism of young hypophysectomized rats fed by stomach tube. *Endocrinology, 33:*87, 1943.
6. Soskin, S., and R. Levine: A relationship between the blood sugar level and the rate of sugar utilization, affecting the theories of diabetes. *Am. J. Physiol., 120:*761, 1937.
7. Price, W. H., C. F. Cori, and S. P. Colowick: The effect of anterior pituitary extract and of insulin on the hexokinase reaction. *J. Biol. Chem., 160:*633, 1945.
8. Rice, L., and E. A. Evans, Jr.: *In vitro* effect of insulin in pigeon breast muscle. *Science, 97:*470, 1943.
9. Biskind, M. S., and H. Schreier: On the significance of nutritional deficiency in diabetes. *Exp. Med. & Surg., 3:*299, 1945.
10. Best, C. H., R. E. Haist, and J. H. Ridout: Diet and the insulin content of pancreas. *J. Physiol. 97:*107, 1939.
11. Lukens, F. D. W.: The pathogenesis of diabetes mellitus. *Yale J. Biol. Med., 16:*301, 1944.
12. Houssay, B. A.: Thyroid and metathyroid diabetes. *Endocrinology, 35:*158, 1944.
13. Banerjee, S.: Vitamin C and carbohydrate metabolism; effect of vitamin C on glucose tolerance test in guinea pigs. *Ann. Biochem. Exp. Med., 3:*157, 1943.
14. Banerjee, S.: Vitamin C and carbohydrate metabolism; effect of vitamin C on insulin content of pancreas of guinea pigs. *Ann. Biochem. Exp. Med., 4:*33, 1944.
15. Haist, R. E.: Factors affecting the insulin content of the pancreas. *Physiol. Rev., 24:*409, 1944.

16. Althausen, T. L., and M. Stockholm: Influence of thyroid gland on absorption in the digestive tract. *Am. J. Physiol., 123:*577, 1938.
17. Althausen, T. L.: Disturbance of carbohydrate metabolism in hyperthyroidism. Nature and Management. *J.A.M.A., 115:*101, 1940.
18. Russell, J. A.: The effect of thyroxin on the carbohydrate metabolism of hypophysectomized rats. *Am. J. Physiol., 122:*547, 1938.
19. Scow, R. O., and W. Marx: Response to pituitary growth hormone of rats thyroidectomized on the day of birth. *Anat. Rec., 91:*227, 1945.
20. Marx, W., M. E. Simpson, and H. M. Evans: Synergism between thyrotrophic and growth hormones of pituitary. *Proc. Soc. Exp. Biol. Med., 49:*594, 1942.
21. Drill, V. A.: The calorie intake and weight balance of hyperthyroid dogs in relation to vitamin B_1 and yeast. *Am. J. Physiol., 132:*629, 1941.
22. Drill, V. A., and C. B. Shaffer: Effect of vitamin B_1 and yeast on calorie intake and weight balance of hyperthyroid dogs. *Endocrinology, 31:*567, 1942.
23. Kunde, M. M.: Studies on experimental cretinism. III. Nutritional disturbances, pellagra and xeropthalmia. *Proc. Soc. Exp. Biol. Med., 23:*812, 1926.
24. Fasold, H. and E. R. Heidemann: Uber die Gelbfärbung der Milch thyreopriver Ziegen., *Ztschr. f. d. ges. exper. Med., 92:*53, 1933.
25. Anderson, H. H., and M. H. Soley: Effects of carotenemia on function of thyroid and liver. *Am. J. M. Sc., 195:*313, 1938.
26. Drill, V. A.: Interrelations between thyroid function and vitamin metabolism. *Physiol. Rev., 23:*355. 1943.
27. Hundhausen, G.: Influence of reduced food intake on thyroid and thyrotrophic hormone of the anterior hyophysis. *Arch. f. exp. Path. u. Pharm., 192:*634, 1939.
28. McCarrison, R.: Pathogenesis of deficiency disease. XI. Observations on fat-excess in relation to iodine requirements and to the thyroid gland. *Ind. J. Med. Res., 11:*1, 1923.
29. Eufinger, H., and J. Gottlieb: Wirkungskoeffizienten des thyroxineffektes im biologischen Versuch. *Klin. Wchnschr., 12:*1397, 1933.
30. Chesney, A. M., T. A. Clawson, and B. Webster: Endemic goitre in rabbits. I. Incidence and characteristics. *Bull. Johns Hopkins Hosp., 43:*261, 1928.

31. Sharpless, G. R., J. Pearsons, and G. Prato: Production of goiter in rats with raw and with treated soy bean flour. *J. Nutrition, 17:* 545, 1939.
32. Hercus, C. E., and H. D. Purves: Studies on endemic and experimental goiter. *J. Hyg., 36:*182, 1936.
33. Marine, D., E. J. Bauman, A. W. Spence, and A. Cipra: Further studies on etiology of goiter with particular reference to the action of cyanides. *Proc. Soc. Exp. Biol. & Med., 29:*772, 1932.
34. Astwood, E. B.: The chemical nature of compounds which inhibit the function of the thyroid gland. *J. Pharmacol. & Exp. Therap., 78:*79, 1943.
35. Gordon, A. S., E. D. Goldsmith, and H. A. Charipper: Effects of para aminobenzoic acid and thiouracil on thyroid function and resistance to low pressures. *Endocrinology, 37:*223, 1945.
36. Gassner, F. X.: The effect of estrogens on the thyroid. *J. Clin. Endocrinology, 6:*460, 1946.
37. Eversole, W. J.: Relation of carbohydrate-deficient diets to the effectiveness of the hormones of the adrenal cortex. *Endocrinology, 37:*450, 1945.
38. Segaloff, A.: Effect of diet on growth and survival of adrenalectomized rats treated with desoxycorticosterone acetate pellets. *Proc. Central Soc. Clin. Res., 18:*27, 1945.
39. Samuels, L. T., and R. M. Reinecke: Unpublished data.
40. Samuels, L. T., and R. F. Conant: The adrenals and the mobilization of stored fat from diets containing different fats. *J. Biol. Chem., 152:*173, 1944.
41. Daft, F. S., and W. H. Sebrell: Hemorrhagic adrenal necrosis in rats on deficient diets. *Pub. Health Rep., 54:*2247, 1939.
42. Gaunt, R., M. Liling, and C. W. Mushett: Disturbances of water metabolism in vitamin deficiencies and effects of adrenal cortical hormones. *Endocrinology, 38:*127, 1946.
43. Ralli, E. P., and I. Graef: Stimulating effect of adrenalectomy on hair growth and melanin deposition in black rats fed diets adequate and deficient in the filtrate factors of vitamin B_1. *Endocrinology, 32:*1, 1943.
44. Ralli, E. P. and I. Graef: The effects of the synthetic and natural hormone of the adrenal cortex on melanin deposition in adrenalectomized black rats fed diets adequate and deficient in the filtrate factors of vitamin B_1. *Endocrinology, 37:*252, 1945.

45. TEPPERMAN, J., F. L. ENGEL, and C. N. H. LONG: Effect of high protein diets on size and activity of the adrenal cortex in the albino rat. *Endocrinology. 32:*403, 1943.

46. INGLE, D. J., G. B. GINTHER, and J. NEZAMIS: Effect of diet in rats on adrenal weights and on survival following adrenalectomy. *Endocrinology, 32:*410, 1943.

47. SAMUELS, L. T.: Unpublished data.

48. BENUA, R. S., and E. HOWARD: The effect of dietary protein on adrenal weights and on growth after unilateral adrenalectomy. *Endocrinology, 36:*170, 1945.

49. SZENT-GYORGYI, A.: Observations on the function of peroxidase systems and the chemistry of the adrenal cortex. Description of a new carbohydrate derivative. *Biochem. J., 22:*1387, 1928.

50. SAYERS, G., M. A. SAYERS, H. L. LEWIS, and C. N. H. LONG: Effect of adrenotrophic hormone on the ascorbic acid and cholesterol content of the adrenal. *Proc. Soc. Exp. Biol. Med., 55:*238, 1944.

51. VANDERLAAN, W. P., and A. BISSELL: Effects of Propylthiouracil and of Potassium Thiocyanate on the Uptake of Iodine by the Thyroid Gland of the Rat. *Endocrinology, 39:*157, 1946.

52. SEALOCK, R. R., and H. E. SILBERSTEIN: The control of experimental alcaptonuria by means of vitamin C. *Science, 90:*517, 1939.

53. LEVINE, S. Z., E. MARPLES, and H. H. GORDON: A defect in the metabolism of tyrosine and phenylalanine in premature infants. I. Identification and assay of intermediary products. *J. Clin. Invest., 20:*199, 1941.

54. DEUEL, H. J., JR., and M. GULICK: Studies on ketosis. I. The sexual variation in starvation ketosis. *J. Biol. Chem., 96:*25, 1932.

55. BUTTS, J. S., and H. J. DEUEL, JR.: Sexual variation in carbohydrate metabolism. II. Metabolism of diacetic acid in fasting rats and guinea pigs. *J. Biol. Chem., 100:*415, 1933.

56. INGLE, D. J.: Diabetogenic effect of stilbestrol in force-fed normal and partially depancreatized rats. *Endocrinology, 29:*838, 1941.

57. INGLE, D. J.: The diabetogenic effect of diethylstilbestrol in adrenalectomized-hypophysectomized-partially depancreatized rats. *Endocrinology, 34:*361, 1944.

58. GARDNER, W. U., and C. A. PFEIFFER: Influence of estrogens and androgens on the skeletal system. *Physiol. Rev., 23:*139, 1943.

59. SILBERBERG, M., and R. SILBERBERG: Effect of progesterone on grow-

ing cartilage and bone in immature guinea pigs. *Arch. Path., 31:*85, 1941.

60. Hertz, R., R. M. Fraps, and W. H. Sebrell: Induction of avidin formation in the avian oviduct by stilbestrol plus progesterone. *Proc. Soc. Exper. Biol. Med., 52:*142, 1943.
61. Ershoff, B. H., and H. J. Deuel, Jr.: Beneficial effects of yeast on body and gonadal weights of rats fed alpha-estradiol. *Am. J. Physiol., 145:*465, 1946.
62. Hertz, R.: The quantitative relationship between stilbestrol response and dietary "folic acid" in the chick. *Endocrinology, 37:*1, 1945.
63. Nelson, M. M., and H. M. Evans: Pantothenic acid deficiency and reproduction in the rat. *J. Nutrition, 31:*497, 1946.
64. Richter, C. P., and B. Barelare, Jr.: Persistence of four to five-day activity cycles in vitamin A deficient rats with constant cornification of the vaginal epithelium. *Endocrinology, 24:*364, 1939.
65. Sherwood, T. C., O. R. Depp, G. P. Birge, and H. B. Dotson: Further studies on the effect of excessive vitamin A on the oestrous cycle of the rat. *J. Nutrition, 14:*481, 1937.
66. Burrill, M. W., and R. R. Greene: Vitamin A and the vaginal response to sex hormones in the rat. *Endocrinology, 28:*765, 1941.
67. Brody, H., and S. Goldman: Relationship of vitamin A and estrogens. *Endocrinology, 29:*164, 1941.
68. Poumeau-Delille, G.: Endocrine reactions of rat and guinea pig after excessive doses of vitamin A. *Compte. R. Soc. Biol., 137:*373, 1943.
69. Giroud, A., and C. P. Leblond: Localisations electives de l'acide ascorbique ou vitamine C (cortex surrenal, testicule, corps jaune, hypophyse). *Arch. d'Anat. Micr., 31:*111, 1935.
70. Giroud, A., R. Ratsimamanga, C. P. Leblond, and M. Rabinowicz: Relations between function of the ovary and vitamin C. *Gyn. et. Obst., 35:*424, 1937.
71. Saffry, O. B., and J. C. Finerty: Injection of corpora lutea extract in pregnant guinea pigs on a vitamin C-limited diet. *Tr. Kans. Acad. Sci., 42:*483, 1939.
72. Ingier, A.: A study of Barlow's disease experimentally produced in foetal and new-born guinea pigs. *J. Exp. Med., 21:*525, 1915.
73. Israel, S. L., and D. R. Meranze: Progesterone-like effect of ascorbic acid (vitamin C) on the endometrium. *Endocrinology, 29:*210, 1941 .

74. KORENCHEVSKY, V., and K. HALL: The interrelationship between vitamins B and C and the female sex hormones in their action on the sex organs of the ovariectomized rat. *J. Path. Bact., 57:*141, 1945.

75 LEY, L.: Ueber die Behandlung des habituellen Abortus mit vitamin C. *Munchen. med. Wchnschr., 84:*1814, 1937.

76. KENYON, A. T.: The comparative metabolic influences of the testicular and ovarian hormones in man. *Biol. Symp., 9:*11, 1942.

77. KENYON, A. T., K. KNOWLTON, and I. SANDIFORD: The anabolic effects of the androgens and somatic growth in man. *Ann. Int. Med., 20:*632, 1944.

78. ZONDEK, B.: Fate of follicular hormone in the living body. *Scand. Arch. Physiol., 70:*133, 1934; *Lancet, 227:*356, 1934.

79. ZONDEK, B.: *Genital Functions and Their Hormonal Regulation.* Williams & Wilkins, 1941.

80. TALBOT, N. B.: The inactivation of endogenous estrogen by the liver. *Endocrinology, 25:*601, 1939.

81. BISKIND, M. S., and G. R. BISKIND: Effect of vitamin B complex deficiency on the inactivation of estrone in the liver. *Endocrinology, 31:*109, 1942.

82. SEGALOFF, A., and A. SEGALOFF: The role of the vitamins of the B-complex in estrogen metabolism. *Endocrinology, 34:*346, 1944.

83. UNNA, K., H. O. SINGHER, C. J. KENSLER, H. C. TAYLOR, JR., and C. P. RHOADS: Effect of dietary protein on liver riboflavin levels and on inactivation of estradiol by liver. *Proc. Soc. Exp. Biol. Med., 55:*254, 1944.

84. DRILL, V. A., and C. A. PFEIFFER: Effect of vitamin B complex deficiency, controlled inanition and methionine on inactivation of estrogen by the liver. *Endocrinology, 38:*300, 1946.

85. GYORGY, P.: Inactivation of estrone by liver. Assay method *in vivo* for dietary hepatic injury in rats. *Proc. Soc. Exp. Biol. Med., 60:* 344, 1945.

86. GLASS, S. J., H. A. EDMONDSON, and S. N. SOLL: Sex hormone changes associated with liver disease. *Endocrinology, 27:*749, 1940.

87. BISKIND, M. S., and G. R. BISKIND. Inactivation of testosterone propionate in the liver during vitamin B complex deficiency. Alteration of the estrogen-androgen equilibrium. *Endocrinology, 32:*97, 1943.

88. Samuels, L. T., and C. McCaulay: Inactivation of testosterone by human liver tissue. *J. Clin. Endocrinology.* (In Press.)
89. Burrill, M. W., and R. R. Greene: The liver and the adrenal androgen of the rat. *Endocrinology, 28:*874, 1941.
90. Kochakian, C. D., A. L. Haskins, and R. A. Bruce: The site of metabolism of progesterone in the rabbit. *Am. J. Physiol., 142:*326, 1944.
91. Burrill, M. W., and R. R. Greene: Capacity of rat's liver to inactivate desoxycorticosterone acetate. *Endocrinology, 30:*142, 1942.
92. Samuels, L. T., and C. McCaulay: An enzyme system in the liver tissue which destroys alpha-beta unsaturated ketone groups in steroids. (In press.)
93. Samuels, L. T., R. M. Reinecke, and H. A. Ball: Balance studies in hypophysectomized and normal rats fed on equicaloric high carbohydrate and high fat diets. *Endocrinology, 31:*35, 1942.
94. Marx, W., V. V. Herring, and H. M. Evans: Hypoglycemic effects of growth hormone in fasting hypophysectomized rats. *Am. J. Physiol., 141:*88, 1944.
95. Evans, H. M., and J. A. Long: The effect of the anterior lobe of the hypophysis administered intraperitoneally on growth, maturity and the estrous cycles of the rat. *Anat. Rec., 21:*62, 1921.
96. Marx, W., E. Anderson, C. T. O. Fong, and H. M. Evans: Effect of growth hormone on glycosuria of fed partially depancreatized rats. *Proc. Soc. Exp. Biol. Med., 53:*38, 1943.
97. Mirsky, I. A., and S. Swadesh: The influence of the anterior pituitary gland on protein metabolism. *Am. J. Physiol., 123:*148, 1938.
98. Gaebler, O. H., and A. R. Robinson: Effects of pancreas and adrenals upon production of nitrogen storage with pituitary preparations. *Endocrinology, 30:*627, 1942.
99. Ershoff, B. H., and H. J. Deuel, Jr.: The effect of growth hormone on the vitamin A-deficient rat. *Endocrinology, 36:*280, 1945.
100. Zimmer, R., J. Weill, and M. Dubois: Nutritional situation in camps of the unoccupied zone of France in 1941 and 1942 and its consequences. *New England J. Med., 230:*303, 1944.
101. Margitay-Becht, E., and E. Wallner: Changes in weight in rats in a state of avitaminosis and treated with growth hormone. *Ztschr. f. Vitaminforsch. 6:*119, 1937.
102. Houssay, B. A., and A. Biasotti: Le diabète pancréatique des chiens hypophysectomisés. *Compt. rend. Soc. biol., 105:*121, 1930.

103. YOUNG, F. G.: Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet, 2:*372, 1937.

104. JACKSON, C. M.: *The Effects of Inanition and Malnutrition upon Growth and Structure.* Philadelphia, P. Blakiston's Son and Co., 1925.

105. MASON, K. E., and J. M. WOLFE: The physiological activity of the hypophysis of rats under various experimental conditions. *Anat. Rec., 45:*232, 1930.

106. MOORE, C. R., and L. T. SAMUELS: The action of testis hormone in correcting changes induced in the rat prostate and seminal vesicles by vitamin B deficiency or partial inanition. *Am. J. Physiol., 96:* 278, 1931.

107. DRILL, V. A., and M. W. BURRILL: Effect of thiamin deficiency and controlled inanition on ovarian function. *Endocrinology, 35:*187, 1944.

108. GUILBERT, H. R., and H. GOSS: Some effects of restricted protein intake on the estrous cycle and gestation in the rat. *J. Nutrition, 5:*251, 1932.

109. PEARSON, P. B.: The effect of a lysine-deficient diet on the estrous cycle. *Am. J. Physiol, 118:*786, 1937.

110. MULINOS, M. G., and L. POMERANTZ: Pseudohypophysectomy. A condition resembling hypophysectomy produced by malnutrition. *J. Nutrition, 19:*493, 1940.

111. MULINOS, M. G., and L. POMERANTZ: Hormonal influences on the weight of the adrenal in inanition. *Am. J. Physiol., 132:*368, 1941.

112. SELYE, H.: Mont Tremblant Conference, 1945.

113. MARTIN, R. W.: Vitamin-free diet and insulin action. *Ztschr. f. physiol. Chem., 248:*242, 1937.

114. ELSOM, K. O., F. D. W. LUKENS, E. H. MONTGOMERY, and L. JONAS: Metabolic disturbances in experimental human vitamin B deficiency. *J. Clin. Invest., 19:*153, 1940.

115. BISKIND, M. S., Nutritional deficiency in the etiology of menorrhagia, metrorrhagia, cystic mastitis and premenstrual tension; treatment with vitamin B complex. *J. Clin. Endocrinology, 3:*227, 1943.

116. BISKIND, M. S., and H. C. FALK: Nutritional therapy of infertility in the male, with special reference to the vitamin B complex and vitamin E. *J. Clin. Endocrinology, 3:*148, 1943.

117. STUART, H. C.: Studies on the nutritional state of children in unoccupied France in the fall of 1942. *J. Pediat., 25:*257, 1944.

118. TAUBER, J.: Netherland children in England. *Brit. Med. J., 1:*486, 1945.

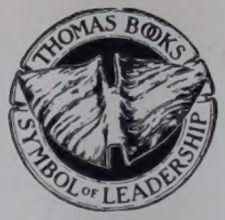
This Book

NUTRITION AND HORMONES

By

LEO T. SAMUELS, PH.D.

was set, printed, and bound by the Collegiate Press of Menasha, Wisconsin. The type face is Linotype Garamond set 11 point on 13 point. The type page is 25 × 43 picas. The page size is 5½ × 8½. The text paper is 70-lb. white Deep Falls Enamel. The cover is No. 25, Black Pajco Lexide, embossing pattern No. 32, TT.



With THOMAS BOOKS careful attention is given to all details of manufacturing and design. It is the Publisher's desire to present books that are satisfactory as to their physical qualities and artistic possibilities and appropriate for their particular use. THOMAS BOOKS will be true to those laws of quality that assure a good name and good will.